=> fil reg
FILE 'REGISTRY' ENTERED AT 06:40:37 ON 14 AUG 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 13 AUG 2003 HIGHEST RN 566135-25-9
DICTIONARY FILE UPDATES: 13 AUG 2003 HIGHEST RN 566135-25-9

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2003

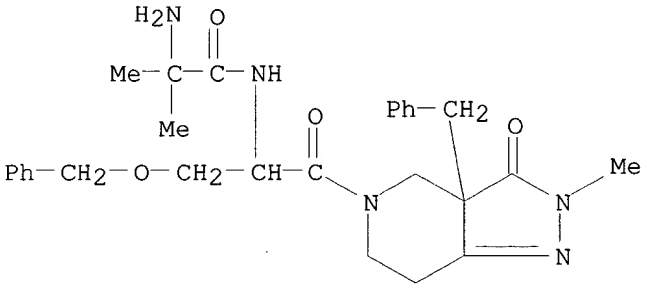
Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=> d ide can tot

L28 ANSWER 1 OF 15 REGISTRY COPYRIGHT 2003 ACS on STN
RN 219323-99-6 REGISTRY
CN Propanamide, 2-amino-N-[2-[2,3,3a,4,6,7-hexahydro-2-methyl-3-oxo-3a-(phenylmethyl)-5H-pyrazolo[4,3-c]pyridin-5-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF **C28 H35 N5 O4**
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1947 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
1 REFERENCES IN FILE CAPLUS (1947 TO DATE)

REFERENCE 1: 130:95850

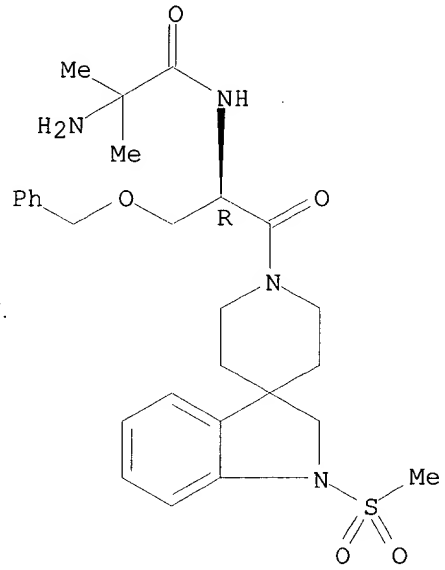
L28 ANSWER 2 OF 15 REGISTRY COPYRIGHT 2003 ACS on STN
RN 194979-53-8 REGISTRY
CN Propanamide, 2-amino-N-[2-[1,2-dihydro-1-(methylsulfonyl)spiro[3H-indole-3,4'-piperidin]-1'-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl-, (R)-, monomethanesulfonate, hydrate (2:7) (9CI) (CA INDEX NAME)

FS STEREOSEARCH
MF C27 H36 N4 O5 S . C H4 O3 S . 7/2 H2 O
SR CA
LC STN Files: CA, CAPLUS

CM 1

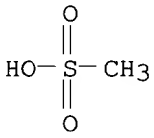
CRN 159634-47-6
CMF C27 H36 N4 O5 S

Absolute stereochemistry.



CM 2

CRN 75-75-2
CMF C H4 O3 S



1 REFERENCES IN FILE CA (1947 TO DATE)
1 REFERENCES IN FILE CAPLUS (1947 TO DATE)

REFERENCE 1: 127:225180

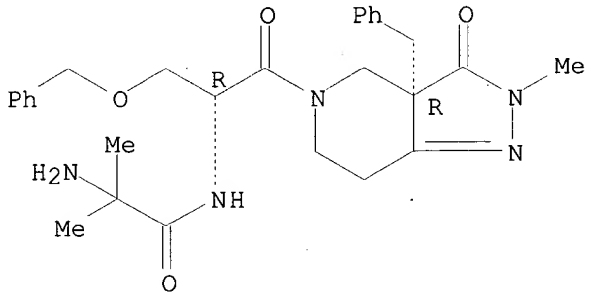
L28 ANSWER 3 OF 15 REGISTRY COPYRIGHT 2003 ACS on STN
RN 193273-69-7 REGISTRY
CN Propanamide, 2-amino-N-[(1R)-2-[(3aR)-2,3,3a,4,6,7-hexahydro-2-methyl-3-oxo-3a-(phenylmethyl)-5H-pyrazolo[4,3-c]pyridin-5-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl-, (2R,3R)-2,3-dihydroxybutanedioate (1:1) (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Propanamide, 2-amino-N-[2-[2,3,3a,4,6,7-hexahydro-2-methyl-3-oxo-3a-(phenylmethyl)-5H-pyrazolo[4,3-c]pyridin-5-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl-, [R-(R*,R*)]-,

[R-(R*,R*)]-2,3-dihydroxybutanedioate (1:1)
OTHER NAMES:
CN Capromorelin tartrate
CN CP 424391-18
FS STEREOSEARCH
MF C28 H35 N5 O4 . C4 H6 O6
SR CA
LC STN Files: BIOSIS, CA, CAPLUS, DRUGUPDATES, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL

CM 1

CRN 193273-66-4
CMF C28 H35 N5 O4

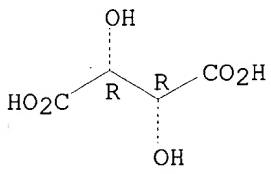
Absolute stereochemistry.



CM 2

CRN 87-69-4
CMF C4 H6 O6

Absolute stereochemistry.



8 REFERENCES IN FILE CA (1947 TO DATE)
8 REFERENCES IN FILE CAPLUS (1947 TO DATE)

REFERENCE 1: 138:378539

REFERENCE 2: 138:363215

REFERENCE 3: 136:273229

REFERENCE 4: 136:236844

REFERENCE 5: 136:221723

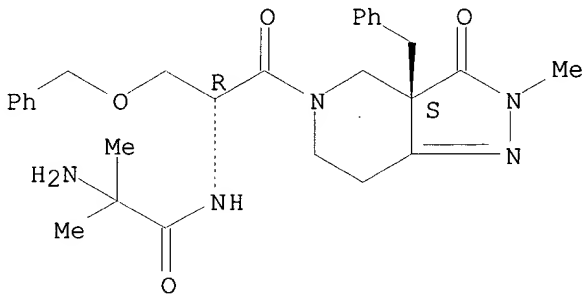
REFERENCE 6: 133:193497

REFERENCE 7: 130:95850

REFERENCE 8: 127:149410

L28 ANSWER 4 OF 15 REGISTRY COPYRIGHT 2003 ACS on STN
RN 193273-68-6 REGISTRY
CN Propanamide, 2-amino-N-[(1R)-2-[(3aS)-2,3,3a,4,6,7-hexahydro-2-methyl-3-oxo-3a-(phenylmethyl)-5H-pyrazolo[4,3-c]pyridin-5-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Propanamide, 2-amino-N-[2-[2,3,3a,4,6,7-hexahydro-2-methyl-3-oxo-3a-(phenylmethyl)-5H-pyrazolo[4,3-c]pyridin-5-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl-, [R-(R*,S*)]-
FS STEREOSEARCH
MF **C28 H35 N5 O4**
CI COM
SR CA
LC STN Files: CA, CAPLUS, DRUGUPDATES, TOXCENTER, USPAT2, USPATFULL

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2 REFERENCES IN FILE CA (1947 TO DATE)
2 REFERENCES IN FILE CAPLUS (1947 TO DATE)

REFERENCE 1: 130:95850

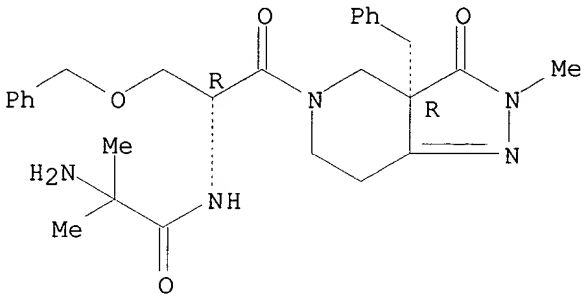
REFERENCE 2: 127:149410

L28 ANSWER 5 OF 15 REGISTRY COPYRIGHT 2003 ACS on STN
RN 193273-67-5 REGISTRY
CN Propanamide, 2-amino-N-[(1R)-2-[(3aR)-2,3,3a,4,6,7-hexahydro-2-methyl-3-oxo-3a-(phenylmethyl)-5H-pyrazolo[4,3-c]pyridin-5-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl-, monomethanesulfonate (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Propanamide, 2-amino-N-[2-[2,3,3a,4,6,7-hexahydro-2-methyl-3-oxo-3a-(phenylmethyl)-5H-pyrazolo[4,3-c]pyridin-5-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl-, [R-(R*,R*)]-, monomethanesulfonate
FS STEREOSEARCH
MF C28 H35 N5 O4 . C H4 O3 S
SR CA
LC STN Files: CA, CAPLUS, DRUGUPDATES, SYNTHLINE, TOXCENTER, USPAT2, USPATFULL

CM 1

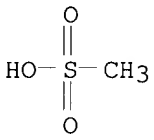
CRN 193273-66-4
CMF C28 H35 N5 O4

Absolute stereochemistry.



CM 2

CRN 75-75-2
CMF C H4 O3 S



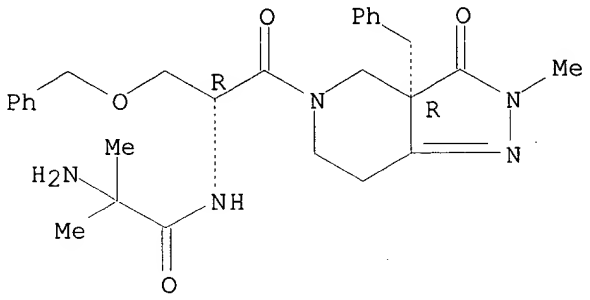
2 REFERENCES IN FILE CA (1947 TO DATE)
2 REFERENCES IN FILE CAPLUS (1947 TO DATE)

REFERENCE 1: 130:95850

REFERENCE 2: 127:149410

L28 ANSWER 6 OF 15 REGISTRY COPYRIGHT 2003 ACS on STN
RN 193273-66-4 REGISTRY
CN Propanamide, 2-amino-N-[(1R)-2-[(3aR)-2,3,3a,4,6,7-hexahydro-2-methyl-3-oxo-3a-(phenylmethyl)-5H-pyrazolo[4,3-c]pyridin-5-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Propanamide, 2-amino-N-[2-[2,3,3a,4,6,7-hexahydro-2-methyl-3-oxo-3a-(phenylmethyl)-5H-pyrazolo[4,3-c]pyridin-5-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl-, [R-(R*,R*)]-
OTHER NAMES:
CN Capromorelin
CN CP 424391
FS STEREOSEARCH
DR 329327-00-6
MF **C28 H35 N5 O4**
CI COM
SR CA
LC STN Files: BIOSIS, CA, CAPLUS, DRUGNL, DRUGUPDATES, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

13 REFERENCES IN FILE CA (1947 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
13 REFERENCES IN FILE CAPLUS (1947 TO DATE)

REFERENCE 1: 138:363215

REFERENCE 2: 138:100848

REFERENCE 3: 136:273229

REFERENCE 4: 136:236844

REFERENCE 5: 136:221723

REFERENCE 6: 136:194460

REFERENCE 7: 135:339292

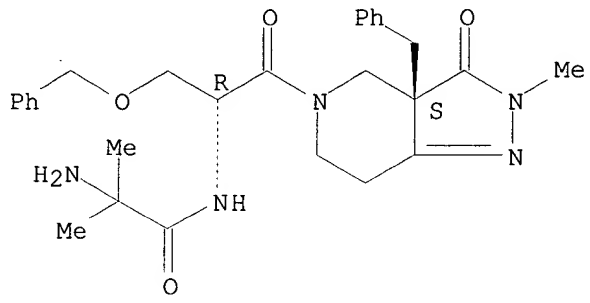
REFERENCE 8: 135:211286

REFERENCE 9: 135:87127

REFERENCE 10: 134:217383

L28 ANSWER 7 OF 15 REGISTRY COPYRIGHT 2003 ACS on STN
RN 193273-65-3 REGISTRY
CN Propanamide, 2-amino-N-[(1R)-2-[(3aS)-2,3,3a,4,6,7-hexahydro-2-methyl-3-oxo-3a-(phenylmethyl)-5H-pyrazolo[4,3-c]pyridin-5-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl-, monohydrochloride (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Propanamide, 2-amino-N-[2-[2,3,3a,4,6,7-hexahydro-2-methyl-3-oxo-3a-(phenylmethyl)-5H-pyrazolo[4,3-c]pyridin-5-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl-, monohydrochloride, [R-(R*,S*)]-
FS STEREOSEARCH
MF C28 H35 N5 O4 . Cl H
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPAT2, USPATFULL
CRN (193273-68-6)

Absolute stereochemistry.



● HCl

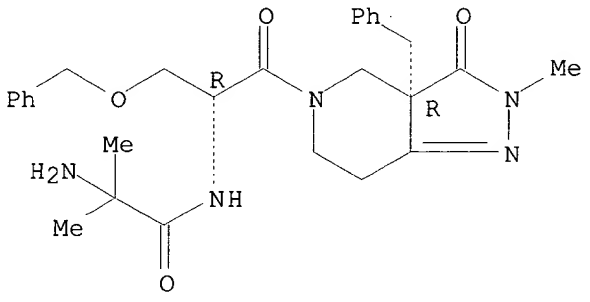
2 REFERENCES IN FILE CA (1947 TO DATE)
2 REFERENCES IN FILE CAPLUS (1947 TO DATE)

REFERENCE 1: 130:95850

REFERENCE 2: 127:149410

L28 ANSWER 8 OF 15 REGISTRY COPYRIGHT 2003 ACS on STN
RN 193270-49-4 REGISTRY
CN Propanamide, 2-amino-N-[(1R)-2-[(3aR)-2,3,3a,4,6,7-hexahydro-2-methyl-3-oxo-3a-(phenylmethyl)-5H-pyrazolo[4,3-c]pyridin-5-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl-, monohydrochloride (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Propanamide, 2-amino-N-[2-[2,3,3a,4,6,7-hexahydro-2-methyl-3-oxo-3a-(phenylmethyl)-5H-pyrazolo[4,3-c]pyridin-5-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl-, monohydrochloride, [R-(R*,R*)]-
FS STEREOSEARCH
MF C28 H35 N5 O4 . Cl H
SR CA
LC STN Files: CA, CAPLUS, SYNTHLINE, TOXCENTER, USPAT2, USPATFULL
CRN (193273-66-4)

Absolute stereochemistry.



● HCl

2 REFERENCES IN FILE CA (1947 TO DATE)

2 REFERENCES IN FILE CAPLUS (1947 TO DATE)

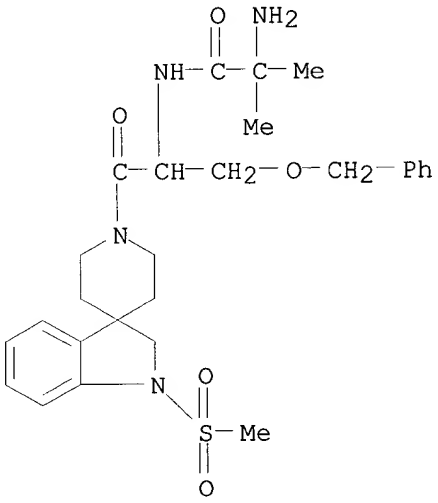
REFERENCE 1: 130:95850

REFERENCE 2: 127:149410

L28 ANSWER 9 OF 15 REGISTRY COPYRIGHT 2003 ACS on STN
RN 191487-52-2 REGISTRY
CN Propanamide, 2-amino-N-[2-[1,2-dihydro-1-(methylsulfonyl)spiro[3H-indole-3,4'-piperidin]-1'-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl-, monomethanesulfonate (9CI) (CA INDEX NAME)
MF C27 H36 N4 O5 S . C H4 O3 S
SR CA
LC STN Files: CA, CAPLUS

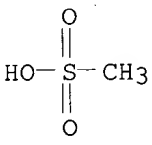
CM 1

CRN 191487-51-1
CMF C27 H36 N4 O5 S



CM 2

CRN 75-75-2
CMF C H4 O3 S

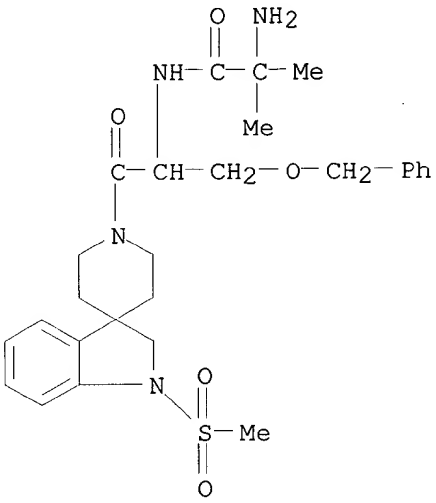


1 REFERENCES IN FILE CA (1947 TO DATE)
1 REFERENCES IN FILE CAPLUS (1947 TO DATE)

REFERENCE 1: 127:70922

L28 ANSWER 10 OF 15 REGISTRY COPYRIGHT 2003 ACS on STN
RN 191487-51-1 REGISTRY
CN Propanamide, 2-amino-N-[2-[1,2-dihydro-1-(methylsulfonyl)spiro[3H-indole-

3,4'-piperidin]-1'-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl-
(9CI) (CA INDEX NAME)
FS 3D CONCORD
MF **C27 H36 N4 O5 S**
CI COM
SR CA



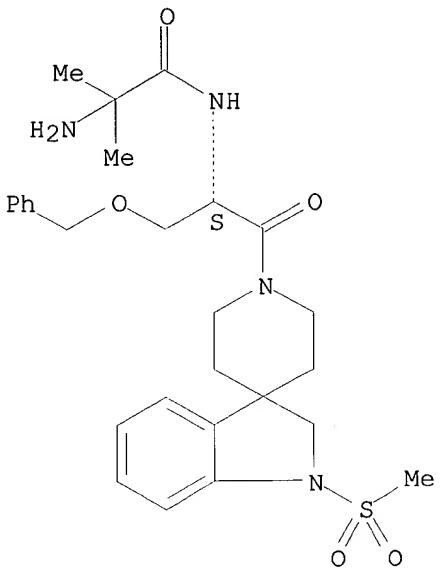
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L28 ANSWER 11 OF 15 REGISTRY COPYRIGHT 2003 ACS on STN
RN 191487-50-0 REGISTRY
CN Propanamide, 2-amino-N-[2-[1,2-dihydro-1-(methylsulfonyl)spiro[3H-indole-3,4'-piperidin]-1'-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl-, (S)-, monomethanesulfonate (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C27 H36 N4 O5 S . C H4 O3 S
SR CA
LC STN Files: CA, CAPLUS

CM 1

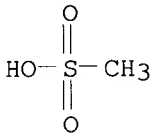
CRN 167386-25-6
CMF C27 H36 N4 O5 S

Absolute stereochemistry.



CM 2

CRN 75-75-2
CMF C H4 O3 S

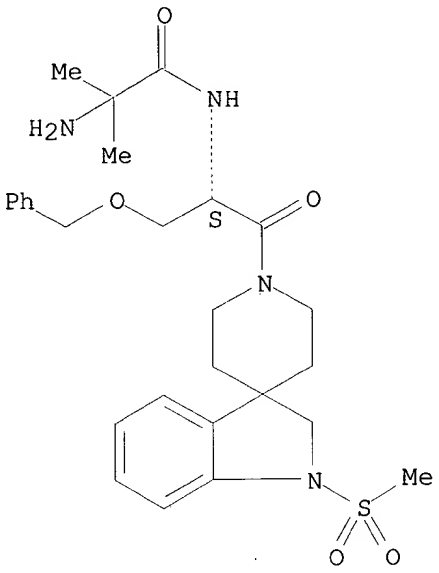


1 REFERENCES IN FILE CA (1947 TO DATE)
1 REFERENCES IN FILE CAPLUS (1947 TO DATE)

REFERENCE 1: 127:70922

L28 ANSWER 12 OF 15 REGISTRY COPYRIGHT 2003 ACS on STN
RN 167386-25-6 REGISTRY
CN Propanamide, 2-amino-N-[2-[1,2-dihydro-1-(methylsulfonyl)spiro[3H-indole-3,4'-piperidin]-1'-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl-, (S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF **C27 H36 N4 O5 S**
CI COM
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1947 TO DATE)
1 REFERENCES IN FILE CAPLUS (1947 TO DATE)

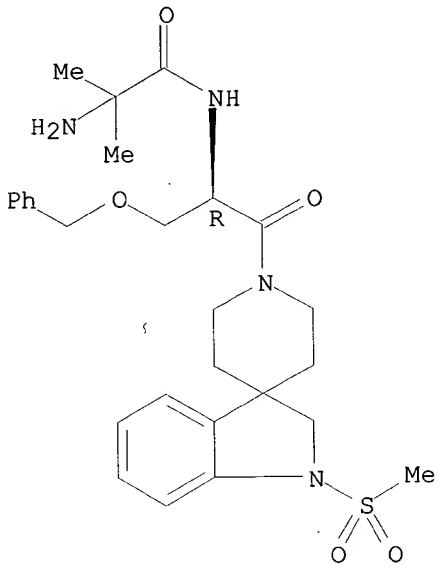
REFERENCE 1: 123:160569

L28 ANSWER 13 OF 15 REGISTRY COPYRIGHT 2003 ACS on STN
RN **159752-10-0** REGISTRY
CN Propanamide, 2-amino-N-[(1R)-2-[1,2-dihydro-1-(methylsulfonyl)spiro[3H-indole-3,4'-piperidin]-1'-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl-, monomethanesulfonate (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Propanamide, 2-amino-N-[2-[1,2-dihydro-1-(methylsulfonyl)spiro[3H-indole-3,4'-piperidin]-1'-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl-, (R)-, monomethanesulfonate
OTHER NAMES:
CN Ibutamoren mesylate
CN MK 677
FS STEREOSEARCH
DR 214962-40-0
MF C27 H36 N4 O5 S . C H4 O3 S
SR CA
LC STN Files: ADISINSIGHT, ADISNEWS, BIOSIS, BIOTECHNO, CA, CAPLUS, CASREACT, CIN, EMBASE, PHAR, PROMT, TOXCENTER, USAN, USPATFULL

CM 1

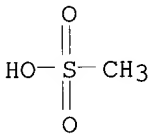
CRN 159634-47-6
CMF C27 H36 N4 O5 S

Absolute stereochemistry.



CM 2

CRN 75-75-2
CMF C H4 O3 S



80 REFERENCES IN FILE CA (1947 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
80 REFERENCES IN FILE CAPLUS (1947 TO DATE)

REFERENCE 1: 139:1182

REFERENCE 2: 138:321564

REFERENCE 3: 138:248763

REFERENCE 4: 138:131394

REFERENCE 5: 137:28593

REFERENCE 6: 136:241940

REFERENCE 7: 136:210055

REFERENCE 8: 136:63596

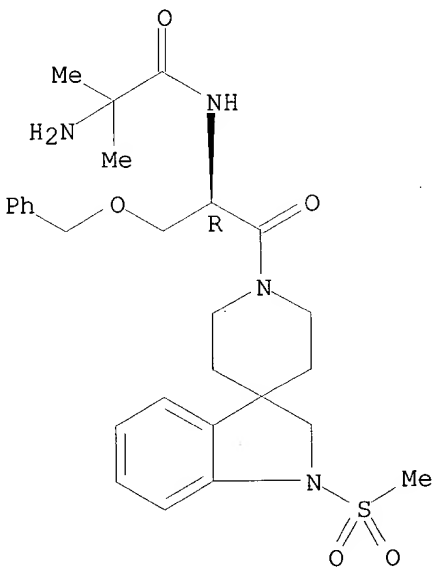
REFERENCE 9: 136:696

REFERENCE 10: 135:353016

L28 ANSWER 14 OF 15 REGISTRY COPYRIGHT 2003 ACS on STN
RN 159634-47-6 REGISTRY

CN Propanamide, 2-amino-N-[(1R)-2-[1,2-dihydro-1-(methylsulfonyl)spiro[3H-indole-3,4'-piperidin]-1'-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Propanamide, 2-amino-N-[2-[1,2-dihydro-1-(methylsulfonyl)spiro[3H-indole-3,4'-piperidin]-1'-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl-, (R)-
OTHER NAMES:
CN Ibutamoren
CN L 163191
FS STEREOSEARCH
MF **C27 H36 N4 O5 S**
CI COM
SR CA
LC STN Files: ADISINSIGHT, ADISNEWS, ANABSTR, BIOSIS, CA, CAPLUS, CASREACT, DDFU, DRUGNL, DRUGU, DRUGUPDATES, IPA, TOXCENTER, USAN, USPATFULL

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

35 REFERENCES IN FILE CA (1947 TO DATE)
2 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
35 REFERENCES IN FILE CAPLUS (1947 TO DATE)

REFERENCE 1: 137:362928

REFERENCE 2: 137:352599

REFERENCE 3: 136:406973

REFERENCE 4: 135:339292

REFERENCE 5: 135:251349

REFERENCE 6: 132:203173

REFERENCE 7: 130:148713

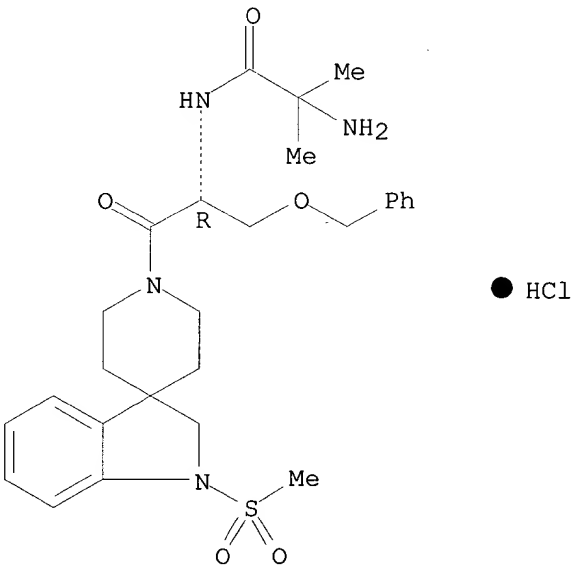
REFERENCE 8: 129:310899

REFERENCE 9: 129:86015

REFERENCE 10: 129:86008

L28 ANSWER 15 OF 15 REGISTRY COPYRIGHT 2003 ACS on STN
RN 159633-92-8 REGISTRY
CN Propanamide, 2-amino-N-[(1R)-2-[1,2-dihydro-1-(methylsulfonyl)spiro[3H-indole-3,4'-piperidin]-1'-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl-, monohydrochloride (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Propanamide, 2-amino-N-[2-[1,2-dihydro-1-(methylsulfonyl)spiro[3H-indole-3,4'-piperidin]-1'-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl-, monohydrochloride, (R)-
FS STEREOSEARCH
MF C27 H36 N4 O5 S . Cl H
SR CA
LC STN Files: CA, CAPLUS, USPATFULL
CRN (159634-47-6)

Absolute stereochemistry.



9 REFERENCES IN FILE CA (1947 TO DATE)
9 REFERENCES IN FILE CAPLUS (1947 TO DATE)

REFERENCE 1: 129:67698

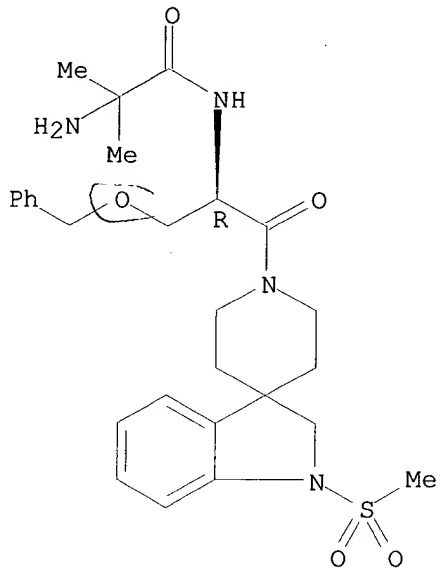
REFERENCE 2: 128:22911

REFERENCE 3: 128:22822

REFERENCE 4: 127:234319

REFERENCE 5: 127:5081

REFERENCE 6: 126:347314



CM 2

CRN 75-75-2
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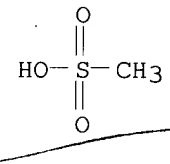

L63 ANSWER 2 OF 3 HCAPLUS COPYRIGHT 2003 ACS on STN
AN 1997:547305 HCAPLUS
DN 127:149410
TI Preparation of nitrogen heterocyclic peptide analogs as growth-hormone secretagogues
IN Carpino, Philip A.; Jardine, Dasilva Paul A.; Lefker, Bruce A.; Ragan, John A.
PA **Pfizer Inc.**, **USA**; Carpino, Philip A.; Jardine, Dasilva Paul A.; Lefker, Bruce A.; Ragan, John A.
SO PCT Int. Appl., 152 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C07K005-06
ICS C07D471-04; C07D521-00; A61K038-05; A61K031-395
CC 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1, 2, 27
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9724369	A1	19970710	WO 1996-IB1353	19961204 <--

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RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

	TW 432073	B	20010501	TW 1996-85113857	19961113 <--
	CA 2241725	AA	19970710	CA 1996-2241725	19961204 <--
	CA 2241725	C	20020618		
	AU 9675850	A1	19970728	AU 1996-75850	19961204 <--
	AU 716934	B2	20000309		
	EP 869968	A1	19981014	EP 1996-938434	19961204 <--
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	CN 1113895	B	20030709		
	JP 11501945	T2	19990216	JP 1996-524124	19961204 <--
	BR 9612465	A	19990713	BR 1996-12465	19961204 <--
	JP 2001213800	A2	20010807	JP 2000-386997	19961204 <--
	RU 2172742	C2	20010827	RU 1998-112108	19961204 <--
	ZA 9610858	A	19980623	ZA 1996-10858	19961223 <--
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	US 6107306	A	20000822	US 1999-259691	19990301 <--
	US 6110932	A	20000829	US 1999-258956	19990301 <--
	US 6124264	A	20000926	US 1999-259776	19990301 <--
	US 6278000	B1	20010821	US 1999-470668	19991222 <--
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	US 2002049196	A1	20020425	US 2000-734274	20001211 <--
	US 6482825	B2	20021119		
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	WO 1996-IB1353	W	19961204		
	US 1998-68566	A3	19980521		
	US 1999-258956	A1	19990301		
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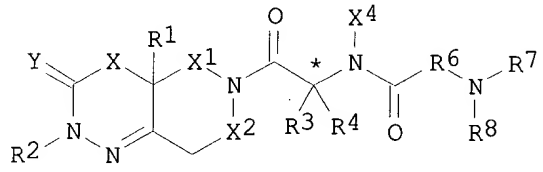
GI					



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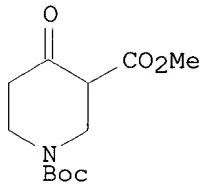

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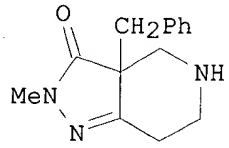

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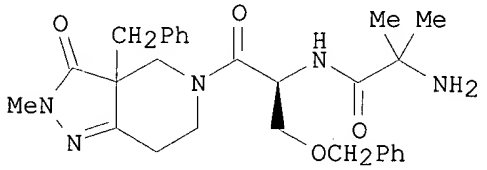

IV

AB Title compds. I [X = CH2, bond; X1, X2 = independently bond, CH2, CH2CH2; Y = O, S; R1 = H, CN, side chain such as (un)substituted (CH2)qN(X6)R, (CH2)tA1, etc.; q = 0-4, t = 0=3; X6 = H, (un)substituted C1-6 alkyl, C3-7 cycloalkyl, etc; A1 = (un)substituted C5-7 cycloalkenyl, Ph, 4-8 membered heterocycle, etc.; R2 = H, (un)substituted C1-8 alkyl, C0-3 alkyl-C3-8 cycloalkyl, C1-4 alkyl-A1; R3 = (un)substituted A1, C1-10 alkyl, C1-6 alkyl-A1, C1-6 alkyl-C3-7 cycloalkyl, etc; R4 = H, (un)substituted C1-6 alkyl, C3-7 cycloalkyl; or R3 and R4 form a ring; X4 = H, C1-6 alkyl; or X4 and R4 form a ring; R6 = bond, Z1(CH2)aC(X5)(X5a)(CH2)b; a = 0-3; b = 0-3; X5, X5a = independently H, CF3, A1, (un)substituted C1-6 alkyl, or form a ring; Z1 = bond, O, NX12, X12 = H, (un)substituted C1-6 alkyl; R7, R8 = independently (un)substituted C1-6 alkyl, or forma a ring] and pharmaceutically-acceptable salts thereof, are growth hormone secretagogues and increase the level of endogenous growth hormone. These compds. are useful for the treatment and prevention of **osteoporosis**, congestive heart failure, frailty assocd. with aging, obesity; accelerating **bone fracture** repair, attenuating protein catabolic response after a major operation, reducing cachexia and protein loss due to chronic illness, accelerating the recovery of burn patients or patients having undergone major surgery; improving muscle strength, mobility, maintenance of skin thickness, metabolic homeostasis or renal homeostasis. These compds. are also useful in treating **osteoporosis** when used in combination with: a bisphosphonate compd. such as alendronate; estrogen, premarin, and optionally progesterone; an estrogen agonist or antagonist; or calcitonin, and pharmaceutical compns. useful therefor. Further, the present invention is directed to pharmaceutical compns. useful for increasing the endogenous prodn. or release of growth hormone in a human or other animal which comprises an effective amt. of a compd. of the present invention and a growth hormone secretagogue selected from GHRP-6, Hexarelin, GHRP-1, growth hormone releasing factor (GRF), IGF-1, IGF-2 or B-HT920. The invention is also directed to intermediates useful in the prepn. of I. Thus, alkylation of oxopiperidinecarboxylate ester II (Boc = Me3CO2C) (prepn. given) with PhCH2Br, followed by cyclocondensation with MeNHNH2 and deprotection gave pyrazolopyridinone III. Amidation of Boc-Aib-D-Ser(CH2Ph)-OH (prepn. given) with III, diastereomer sepn., and deprotection, gave sepd. title compds. IV as their HCl salts.

ST growth hormone secretagogue peptidyl heterocycle prepn; nitrogen heterocycle peptidyl growth hormone secretagogue

IT Peptides, preparation
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(amides, nitrogen heterocyclic; prepn. of nitrogen heterocyclic peptide analogs as growth-hormone secretagogues)

IT Estrogens
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(conjugated; prepn. of nitrogen heterocyclic peptide analogs as growth-hormone secretagogues)

IT Heart, disease
(failure; prepn. of nitrogen heterocyclic peptide analogs as growth-hormone secretagogues)

IT Heterocyclic compounds
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(nitrogen, peptidyl; prepn. of nitrogen heterocyclic peptide analogs as growth-hormone secretagogues)

IT Aging, animal
Obesity
Osteoporosis
(prepn. of nitrogen heterocyclic peptide analogs as growth-hormone

secretagogues)

IT Estrogens
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(prepn. of nitrogen heterocyclic peptide analogs as growth-hormone secretagogues)

IT 193270-48-3P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. of nitrogen heterocyclic peptide analogs as growth-hormone secretagogues)

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193273-84-6P 193273-85-7P 193273-86-8P 193273-87-9P 193273-88-0P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of nitrogen heterocyclic peptide analogs as growth-hormone secretagogues)

IT 57-83-0, Progesterone, biological studies 9002-72-6, Growth hormone
9007-12-9, Calcitonin 9034-39-3, Growth hormone releasing factor
10540-29-1, Tamoxifen 36085-73-1, B-HT920 66376-36-1, Alendronate
67763-96-6, IGF-1 67763-97-7, IGF 2 82413-20-5, Droloxifene
84449-90-1, Raloxifene 87616-84-0 114084-78-5, Ibandronate

116057-75-1, Idoxifene 140703-51-1, Hexarelin 141925-59-9, GHRP 1
180915-78-0 180915-84-8 180915-86-0 180916-14-7 180916-15-8
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RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(prepn. of nitrogen heterocyclic peptide analogs as growth-hormone secretagogues)

IT 193274-35-0P
RL: PUR (Purification or recovery); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
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IT 60-34-4, Methylhydrazine 87-69-4, L-Tartaric acid, reactions 96-32-2, Methyl bromoacetate 153-94-6, D-Tryptophan 302-15-8, Methylhydrazine sulfate 459-46-1, 4-Fluorobenzyl bromide 3364-76-9, 4-Chloromethylthiazole 4377-33-7, 2-Picolyl chloride 4392-24-9, Cinnamyl bromide 4644-61-5 5042-30-8, 2,2,2-Trifluoroethylhydrazine 5241-64-5 6368-20-3 6629-60-3, Ethylhydrazine oxalate 20443-99-6 20570-96-1, Benzylhydrazine dihydrochloride 30992-29-1 32064-67-8, tert-Butylhydrazine 47173-80-8 108554-34-3 112741-50-1 193274-86-1
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of nitrogen heterocyclic peptide analogs as growth-hormone secretagogues)

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(prepn. of nitrogen heterocyclic peptide analogs as growth-hormone secretagogues)

IT **193270-49-4P 193273-65-3P 193273-66-4P**
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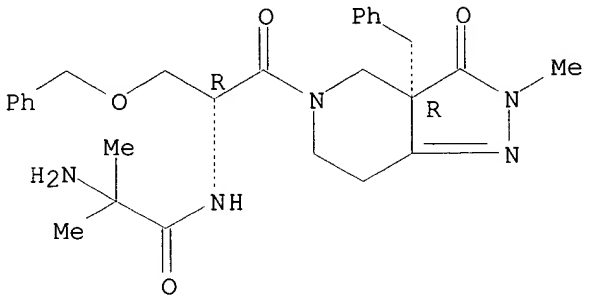
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of nitrogen heterocyclic peptide analogs as growth-hormone secretagogues)

RN 193270-49-4 HCAPLUS

CN Propanamide, 2-amino-N-[(1R)-2-[(3aR)-2,3,3a,4,6,7-hexahydro-2-methyl-3-oxo-3a-(phenylmethyl)-5H-pyrazolo[4,3-c]pyridin-5-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● HCl

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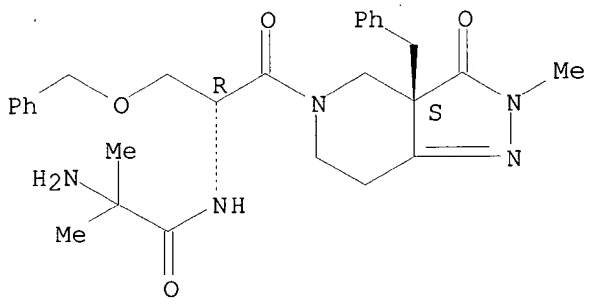
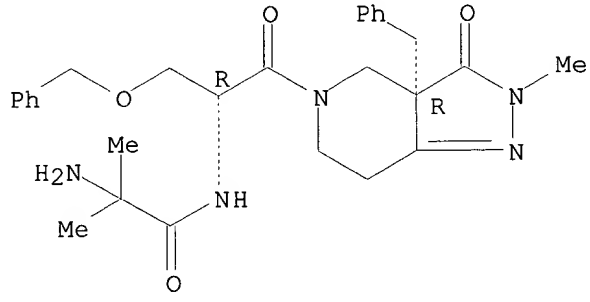
Absolute stereochemistry.



● HCl

RN 193273-66-4 HCAPLUS
CN Propanamide, 2-amino-N-[(1R)-2-[(3aR)-2,3,3a,4,6,7-hexahydro-2-methyl-3-oxo-3a-(phenylmethyl)-5H-pyrazolo[4,3-c]pyridin-5-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

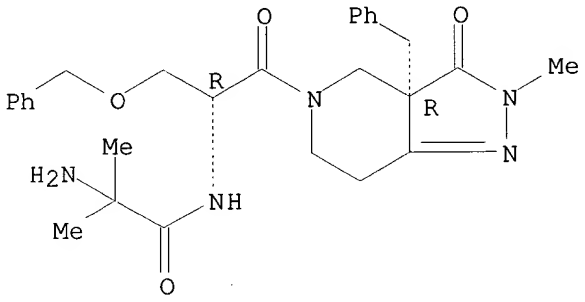


RN 193273-67-5 HCAPLUS
CN Propanamide, 2-amino-N-[(1R)-2-[(3aR)-2,3,3a,4,6,7-hexahydro-2-methyl-3-oxo-3a-(phenylmethyl)-5H-pyrazolo[4,3-c]pyridin-5-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl-, monomethanesulfonate (9CI) (CA INDEX NAME)

CM 1

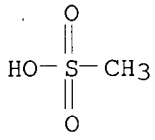
CRN 193273-66-4
CMF C28 H35 N5 O4

Absolute stereochemistry.



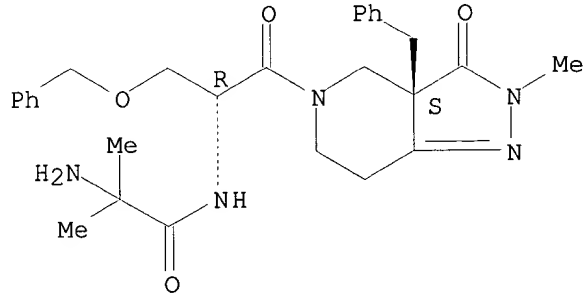
CM 2

CRN 75-75-2
CMF C H4 O3 S



RN 193273-68-6 HCAPLUS
CN Propanamide, 2-amino-N-[(1R)-2-[(3aS)-2,3,3a,4,6,7-hexahydro-2-methyl-3-oxo-3a-(phenylmethyl)-5H-pyrazolo[4,3-c]pyridin-5-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



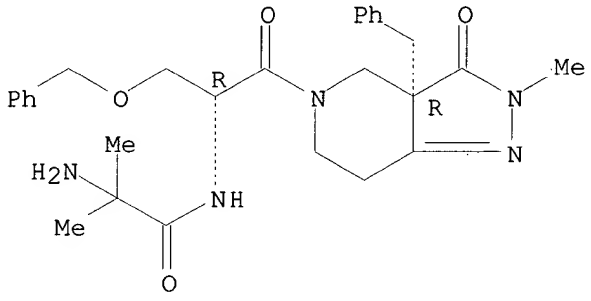
RN 193273-69-7 HCAPLUS
CN Propanamide, 2-amino-N-[(1R)-2-[(3aR)-2,3,3a,4,6,7-hexahydro-2-methyl-3-oxo-3a-(phenylmethyl)-5H-pyrazolo[4,3-c]pyridin-5-yl]-2-oxo-1-

[(phenylmethoxy)methyl]ethyl]-2-methyl-, (2R,3R)-2,3-dihydroxybutanedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 193273-66-4
CMF C28 H35 N5 O4

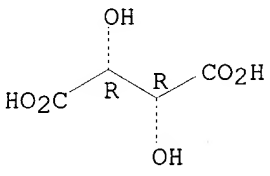
Absolute stereochemistry.



CM 2

CRN 87-69-4
CMF C4 H6 O6

Absolute stereochemistry.



L63 ANSWER 3 OF 3 HCAPLUS COPYRIGHT 2003 ACS on STN
AN 1995:686929 HCAPLUS
DN 123:74929
TI Combination of bisphosphonates and growth hormone secretagogues for treatment of **osteoporosis**, and their preparation
IN Gertz, Barry J.; Rodan, Gideon A.; Smith, Roy G.; Wyvratt, Matthew J.; Patchett, Arthur A.
PA Merck and Co., Inc., USA
SO PCT Int. Appl., 104 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K031-66
ICS A61K031-445
CC 1-12 (Pharmacology)
Section cross-reference(s): 28
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9511029	A1	19950427	WO 1994-US11912	19941018 <--

W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, JP, KG, KR, KZ, LK, LR, LT, LV, MD, MG, MN, NO, NZ, PL, RO, RU, SI, SK, TJ, TT, UA, US, US, UZ

RW: KE, MW, SD, SZ, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

CA 2173333	AA	19950427	CA 1994-2173333	19941018	<--
AU 9480836	A1	19950508	AU 1994-80836	19941018	<--
BR 9407869	A	19961029	BR 1994-7869	19941018	<--
CN 1136278	A	19961120	CN 1994-194311	19941018	<--
HU 75224	A2	19970428	HU 1996-1013	19941018	<--
JP 09504525	T2	19970506	JP 1994-512182	19941018	<--
EP 813414	A1	19971229	EP 1994-931923	19941018	<--

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, SI, LT

FI 9601681	A	19960612	FI 1996-1681	19960417	<--
NO 9601536	A	19960618	NO 1996-1536	19960418	<--
LV 11432	B	19961220	LV 1996-124	19960423	<--

PRAI US 1993-139296	19931019	<--	
US 1994-259091	19940613	<--	
WO 1994-US11912	19941018	<--	

OS MARPAT 123:74929

AB Bisphosphonates in combination with growth hormone secretagogues (Markush included for both bisphosphonates and growth hormone secretagogues) reduce the deleterious effects of **osteoporosis** in elderly patients. Prepn. of selected compds. of the invention is described. The effect of N-[1(R)-((1,2-dihydro-1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1'-yl)carbonyl)-3-phenylpropyl]-2-amino-2-methylpropanamide, alone and in combination with pamidronate (3-amino-1-hydroxypropylidene-1,1-bisphosphonic acid), on **bone** in old female rats was evaluated. Results indicated that the growth hormone secretagogue restored **bone** formation that had been suppressed by the bisphosphonate to control levels. Addnl., the was no difference in **osteoclast** surface (**bone** resorption) as a result of treatment with the growth hormone secretagogue.

ST bisphosphonate growth hormone secretagogue prepn **osteoporosis**

IT **Osteoporosis**
(combination of bisphosphonates and growth hormone secretagogues for treatment of **osteoporosis**, and their prepn.)

IT 40391-99-9, Pamidronic acid
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination of bisphosphonates and growth hormone secretagogues for treatment of **osteoporosis**, and their prepn.)

IT 56-12-2, 4-Aminobutyric acid, reactions 76-83-5, Triphenylmethyl chloride 100-47-0, Benzonitrile, reactions 100-51-6, Benzenemethanol, reactions 107-18-6, 2-Propen-1-ol, reactions 597-43-3, 2,2-Dimethylsuccinic acid 624-31-7, 4-Iodotoluene 26386-88-9, Diphenylphosphoryl azide 30992-29-1 47173-80-8 50893-53-3, 1-Chloroethyl chloroformate 69584-91-4 81445-45-6 82732-07-8 86499-24-3
RL: RCT (Reactant); RACT (Reactant or reagent)
(combination of bisphosphonates and growth hormone secretagogues for treatment of **osteoporosis**, and their prepn.)

IT 18039-42-4P, 5-Phenyltetrazole 51219-55-7P 54043-71-9P 86499-35-6P 87268-78-8P, 5-Phenyl-2-trityltetrazole 124750-51-2P 124750-53-4P 128182-82-1P 137036-55-6P 145457-69-8P 145457-70-1P 159634-86-3P 159634-87-4P 159634-88-5P 159634-96-5P 165125-49-5P 165125-50-8P 165125-51-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(combination of bisphosphonates and growth hormone secretagogues for treatment of **osteoporosis**, and their prepn.)

IT 145455-80-7P
RL: RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use);

BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(combination of bisphosphonates and growth hormone secretagogues for treatment of **osteoporosis**, and their prepn.)

IT 137036-54-5P
RL: SPN (Synthetic preparation); PREP (Preparation)
(combination of bisphosphonates and growth hormone secretagogues for treatment of **osteoporosis**, and their prepn.)

IT 66376-36-1P, Alendronic acid 145455-23-8P 145455-35-2P
159633-92-8P 159633-99-5P **159634-47-6P**
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(combination of bisphosphonates and growth hormone secretagogues for treatment of **osteoporosis**, and their prepn.)

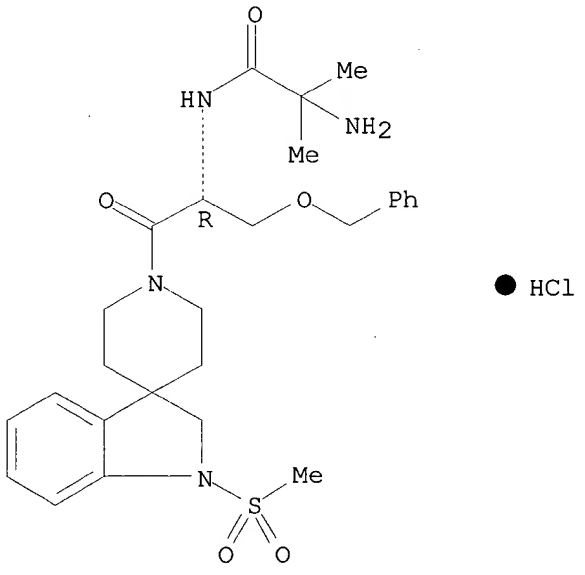
IT 2809-21-4, Etidronic acid 10596-23-3, Clodronic acid 79778-41-9
89987-06-4, Tiludronic acid 105462-24-6, Risedronic acid 114084-78-5
159634-42-1 159634-43-2 159634-44-3 159634-46-5 159634-49-8
159634-50-1 159634-51-2 159634-52-3 159634-53-4 159634-54-5
159634-55-6 159634-56-7 159634-57-8 159634-58-9 **159752-10-0**
165125-48-4
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination of bisphosphonates and growth hormone secretagogues for treatment of **osteoporosis**, and their prepn.)

IT 9002-72-6, Growth hormone
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(secretagogues; combination of bisphosphonates and growth hormone secretagogues for treatment of **osteoporosis**, and their prepn.)

IT **159633-92-8P 159634-47-6P**
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(combination of bisphosphonates and growth hormone secretagogues for treatment of **osteoporosis**, and their prepn.)

RN 159633-92-8 HCAPLUS
CN Propanamide, 2-amino-N-[(1R)-2-[1,2-dihydro-1-(methylsulfonyl)spiro[3H-indole-3,4'-piperidin]-1'-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl-, monohydrochloride (9CI) (CA INDEX NAME)

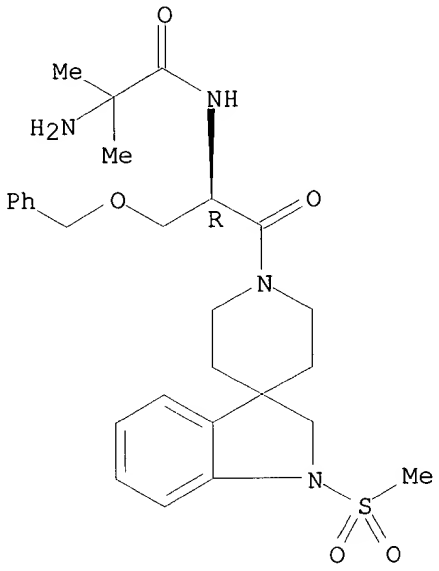
Absolute stereochemistry.



RN 159634-47-6 HCAPLUS

CN Propanamide, 2-amino-N-[(1R)-2-[1,2-dihydro-1-(methylsulfonyl)spiro[3H-indole-3,4'-piperidin]-1'-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **159752-10-0**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination of bisphosphonates and growth hormone secretagogues for treatment of **osteoporosis**, and their prepn.)

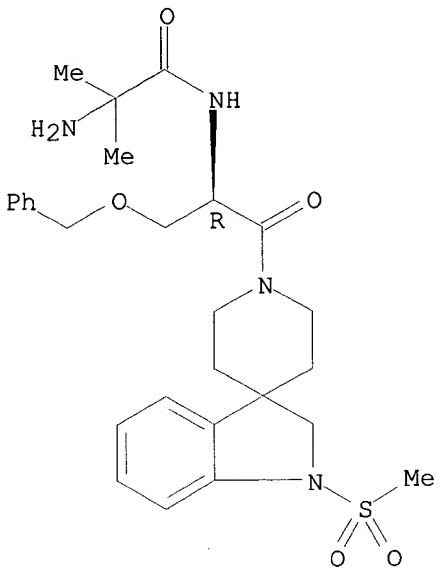
RN 159752-10-0 HCAPLUS

CN Propanamide, 2-amino-N-[(1R)-2-[1,2-dihydro-1-(methylsulfonyl)spiro[3H-indole-3,4'-piperidin]-1'-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl-, monomethanesulfonate (9CI) (CA INDEX NAME)

CM 1

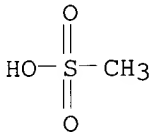
CRN 159634-47-6
CMF C27 H36 N4 O5 S

Absolute stereochemistry.



CM 2

CRN 75-75-2
CMF C H4 O3 S



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CA INDEXING COPYRIGHT (C) 2003 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'USPAT2' ENTERED AT 06:58:35 ON 14 AUG 2003
CA INDEXING COPYRIGHT (C) 2003 AMERICAN CHEMICAL SOCIETY (ACS)

=> d l73 bib ab kwic hitstr tot

L73  ANSWER 1 OF 10  USPATFULL on STN
AN     2002:92672  USPATFULL
TI     Growth-hormone secretagogues
IN     Carpino, Philip A., Groton, CT, UNITED STATES
       DaSilva-Jardine, Paul A., Providence, RI, UNITED STATES
       Lefker, Bruce A., Gales Ferry, CT, UNITED STATES
       Ragan, John A., Gales Ferry, CT, UNITED STATES
PI     US 2002049196      A1   20020425
       US 6482825         B2   20021119
AI     US 2000-734274     A1   20001211 (9)
RLI    Continuation of Ser. No. US 1998-68566, filed on 21 May 1998, ABANDONED
       Continuation of Ser. No. WO 1996-IB1353, filed on 4 Dec 1996, UNKNOWN
PRAI   US 1995-9469P       19951228 (60)                                    <--
DT     Utility
FS     APPLICATION
```

LREP Gregg C. Benson, Pfizer Inc., Patent Department, MS 4159, Eastern Point Road, Groton, CT, 06340
CLMN Number of Claims: 110
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 4938
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention is directed to compounds of the formula ##STR1##

and the pharmaceutically-acceptable salts thereof, where the substituents are as defined in the Specification, which are growth hormone secretogogues and which increase the level of endogenous growth hormone. The compounds of this invention are useful for the treatment and prevention of **osteoporosis**, congestive heart failure, frailty associated with aging, obesity; accelerating **bone fracture** repair, attenuating protein catabolic response after a major operation, reducing cachexia and protein loss due to chronic illness, accelerating wound healing, or accelerating the recovery of burn patients or patients having undergone major surgery; improving muscle strength, mobility, maintenance of skin thickness, metabolic homeostasis or renal homeostasis. The compounds of the present invention are also useful in treating **osteoporosis** when used in combination with: a bisphosphonate compound such as alendronate; estrogen, premarin, and optionally progesterone; an estrogen agonist or antagonist; or calcitonin, and pharmaceutical compositions useful therefor. Further, the present invention is directed to pharmaceutical compositions useful for increasing the endogenous production or release of growth hormone in a human or other animal which comprises an effective amount of a compound of the present invention and a growth hormone secretagogue selected from GHRP-6, Hexarelin, GHRP-1, growth hormone releasing factor (GRF), IGF-1, IGF-2 or B-HT920. The invention is also directed to intermediates useful in the preparation of compounds of formula I.

PRAI US 1995-9469P 19951228 (60) <--
AB . . . increase the level of endogenous growth hormone. The compounds of this invention are useful for the treatment and prevention of **osteoporosis**, congestive heart failure, frailty associated with aging, obesity; accelerating **bone fracture** repair, attenuating protein catabolic response after a major operation, reducing cachexia and protein loss due to chronic illness, accelerating wound. . . maintenance of skin thickness, metabolic homeostasis or renal homeostasis. The compounds of the present invention are also useful in treating **osteoporosis** when used in combination with: a bisphosphonate compound such as alendronate; estrogen, premarin, and optionally progesterone; an estrogen agonist or. . .
SUMM . . . This invention relates to dipeptide compounds which are growth hormone secretagogues and are useful for the treatment and prevention of **osteoporosis**.
SUMM . . . the truncal region. Decreased skeletal and cardiac muscle mass and muscle strength lead to, a significant reduction in exercise capacity. **Bone** density is also reduced. Administration of exogenous growth hormone has been shown to reverse many of the metabolic changes. Additional. . .
SUMM [0012] The compounds of WO 94/11012 and WO 94/13696 are reported to be useful in the treatment of **osteoporosis** in combination with parathyroid hormone or a bisphosphonate.
SUMM [0250] a method for the treatment or prevention of **osteoporosis** which comprises administering to a human or other animal in need of such treatment or prevention an amount of a compound of Formula I which is effective in treating or preventing **osteoporosis**;
SUMM [0251] a method for the treatment or prevention of **osteoporosis** which comprises administering to a human or other animal with **osteoporosis** a combination of a bisphosphonate compound such as

alendronate, and especially preferred is the bisphosphonate compound ibandronate, and a compound. . .

SUMM [0252] a method for the treatment -or prevention of **osteoporosis** which comprises administering to a human or other animal with **osteoporosis** a combination of estrogen or Premarin.RTM. and a compound of Formula I and optionally progesterone;

SUMM [0254] a method for the treatment of **osteoporosis** which comprises administering to a human or other animal with **osteoporosis** a combination of an estrogen agonist or antagonist such as tamoxifen, droloxifene, raloxifene and idoxifene and a compound of Formula. . .

SUMM [0255] a particularly preferred method for the treatment of **osteoporosis** comprises administering to a human or other animal with **osteoporosis** a combination of an estrogen agonist or antagonist such as Cis-6-(4fluoro-phenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5,6,7,8tetrahydro-naphthalene2-ol;

SUMM [0262] a method for the treatment of **osteoporosis** which comprises administering to a human or other animal with **osteoporosis** a combination of calcitonin and a compound of Formula I;

SUMM [0267] In another aspect, this invention provides methods for accelerating **bone fracture** repair, attenuating protein catabolic response after a major operation, reducing cachexia and protein loss due to chronic illness such as. . . effective in promoting release of endogenous growth hormone; of the instant method a preferred method of use is to accelerate **bone fracture** repair or for accelerating the recovery of patients having undergone major surgery.

SUMM . . . efficiency of animals raised for meat production to improve carcass quality; to increase milk production in dairy cattle; improvement of **bone** or wound healing and improvement in vital organ function. The compounds of the present invention by inducing endogenous GH secretion. . .

SUMM . . . Formula I or another compound which exhibits a different activity, e.g., an antibiotic growth permittant or an agent to treat **osteoporosis** or with other pharmaceutically active materials wherein the combination enhances efficacy and minimizes side effects.

SUMM . . . follows: stimulating growth hormone release in elderly humans; treating growth hormone deficient adults; preventing catabolic side effects of glucocorticoids, treating **osteoporosis**, stimulating the immune system, acceleration of wound healing, accelerating **bone fracture** repair, treating growth retardation, treating congestive heart failure as disclosed in PCT publications WO 95/128173 and WO 95/128174 (an example. . . as gastrointestinal surgery; treating intrauterine growth retardation, skeletal dysplasia, hypercortisonism and Cushings syndrome; replacing growth hormone in stressed patients; treating **osteochondrodysplasias**, Noonans syndrome, sleep disorders, Alzheimer's disease, delayed wound healing, and psychosocial deprivation; treating of pulmonary dysfunction and ventilator dependency; attenuating. . . improving muscle strength, increasing muscle mass, mobility, maintenance of skin thickness, metabolic homeostasis, renal hemeostasis in the frail elderly; stimulating **osteoblasts**, **bone** remodelling, and cartilage growth; treating neurological diseases such as peripheral and drug induced neuropathy, Guillian-Barre Syndrome, amyotrophic lateral sclerosis, multiple. . .

SUMM . . . one times the dose levels which are effective when these compounds and secretagogues are used singly. Combined therapy to inhibit **bone** resorption, prevent **osteoporosis**, reduce skeletal **fracture**, enhance the healing of **bone fractures**, stimulate **bone** formation and increase **bone** mineral density can be effectuated by combinations of bisphosphonates and the growth hormone secretagogues of this invention,

see PCT publication. . . The use of bisphosphonates for these utilities has been reviewed, for example, by Hamdy, N.A.T., Role of Bisphosphonates in Metabolic **Bone** Diseases, Trends in Endocrinol. Metab., 1993, 4, pages 19-25. Bisphosphonates with these utilities include but are not limited to alendronate,. . . invention of between 0.01 mg/kg to 20 mg/kg of body weight are administered to patients to obtain effective treatment of **osteoporosis**.

SUMM . . . the second compound of this invention. The term estrogen agonist/antagonist refers to compounds which bind with the estrogen receptor, inhibit **bone** turnover and prevent **bone** loss. In particular, estrogen agonists are herein defined as chemical compounds capable of binding to the estrogen receptor sites in. . . activities are readily determined by those skilled in the art according to standard assays including estrogen receptor binding assays, standard **bone** histomorphometric and densitometer methods (see Eriksen E. F. et al., **Bone** Histomorphometry, Raven Press, New York, 1994, pages 1-74; Grier S. J. et al., The Use of Dual-Energy X-Ray Absorptiometry In Animals, Inv. Radiol., 1996, 31(1):50-62; Wahner H. W. and Fogelman I., The Evaluation of **Osteoporosis**: Dual Energy X-Ray Absorptiometry in Clinical Practice., Martin Dunit Ltd., London 1994, pages 1-296). A variety of these compounds are. . .

SUMM [0314] The amount of the anti-resorptive agent to be used is determined by its activity as a **bone** loss inhibiting agent. This activity is determined by means of an individual compound's pharmacoidnetics and its minimal maximal effective dose in inhibition of **bone** loss using a protocol such as those referenced above.

SUMM [0315] In general an effective dosage for the activities of this invention, for example the treatment of **osteoporosis**, for the estrogen agonists/antagonists (when used in combination with a compound of Formula I of this invention) is in the. . .

CLM What is claimed is:

48. A method for treating or preventing **osteoporosis** which comprises administering to a human or other animal in need of such treatment or prevention an amount of a compound of claim 1 which is effective in treating or preventing **osteoporosis**.

51. A method for accelerating **bone fracture** repair, attenuating protein catabolic response after a major operation, reducing cachexia and protein loss due to chronic illness, accelerating wound. . .

53. A method for the treatment or prevention of **osteoporosis** which comprises administering to a human or other animal with **osteoporosis** a combination of a bisphosphonate compound and a compound of claim 1.

54. A method for the treatment of **osteoporosis** according to claim 53 wherein the bisphosphonate compound is alendronate.

55. A method for the treatment or prevention of **osteoporosis** which comprises administering to a human or other animal with **osteoporosis** a combination of estrogen or Premarin.RTM. and a compound of claim 1 and optionally progesterone.

57. A method for the treatment of **osteoporosis** which comprises administering to a human or other animal with **osteoporosis** a combination of calcitonin and a compound of claim 1.

59. A method for the treatment of **osteoporosis** which comprises administering to a human or other animal with **osteoporosis** a combination of an estrogen agonist or antagonist and a compound of claim 1.

106. A method according to claim 51 wherein the method is for

accelerating **bone fracture** repair.

108. A method for the treatment of **osteoporosis** according to claim 53 wherein the bisphosphonate compound is ibandronate.

IT Aging, animal
IT Obesity
IT **Osteoporosis**
(prepn. of nitrogen heterocyclic peptide analogs as growth-hormone secretagogues)

IT 193270-46-1P 193270-47-2P **193270-49-4P** 193270-50-7P
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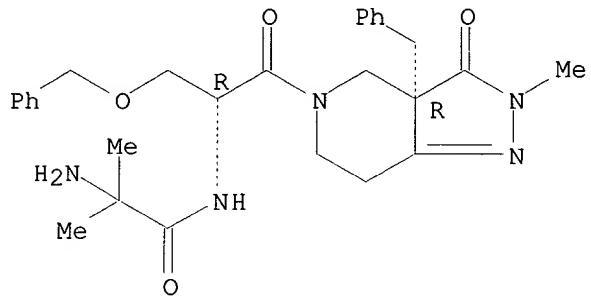
193273-21-1P 193273-22-2P 193273-23-3P 193273-24-4P 193273-25-5P
193273-26-6P 193273-27-7P 193273-29-9P 193273-31-3P 193273-33-5P
193273-35-7P 193273-37-9P 193273-40-4P 193273-42-6P 193273-45-9P
193273-48-2P 193273-50-6P 193273-52-8P 193273-54-0P 193273-56-2P
193273-58-4P 193273-60-8P 193273-62-0P 193273-64-2P
193273-65-3P 193273-66-4P 193273-67-5P
193273-68-6P 193273-69-7P 193273-70-0P 193273-71-1P
193273-72-2P 193273-73-3P 193273-74-4P 193273-76-6P 193273-78-8P
193273-79-9P 193273-80-2P 193273-81-3P 193273-82-4P 193273-83-5P
193273-84-6P 193273-85-7P 193273-86-8P 193273-87-9P 193273-88-0P
(prepn. of nitrogen heterocyclic peptide analogs as growth-hormone secretagogues)

IT **193270-49-4P 193273-65-3P 193273-66-4P**
193273-67-5P 193273-68-6P 193273-69-7P
(prepn. of nitrogen heterocyclic peptide analogs as growth-hormone secretagogues)

RN 193270-49-4 USPATFULL
CN Propanamide, 2-amino-N-[(1R)-2-[(3aR)-2,3,3a,4,6,7-hexahydro-2-methyl-3-oxo-3a-(phenylmethyl)-5H-pyrazolo[4,3-c]pyridin-5-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl-, monohydrochloride (9CI) (CA INDEX NAME)

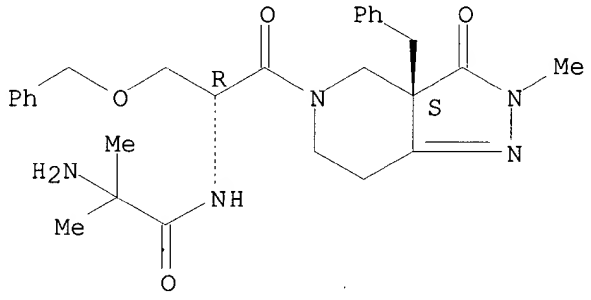
Absolute stereochemistry.



● HCl

RN 193273-65-3 USPATFULL
CN Propanamide, 2-amino-N-[(1R)-2-[(3aS)-2,3,3a,4,6,7-hexahydro-2-methyl-3-oxo-3a-(phenylmethyl)-5H-pyrazolo[4,3-c]pyridin-5-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl-, monohydrochloride (9CI) (CA INDEX NAME)

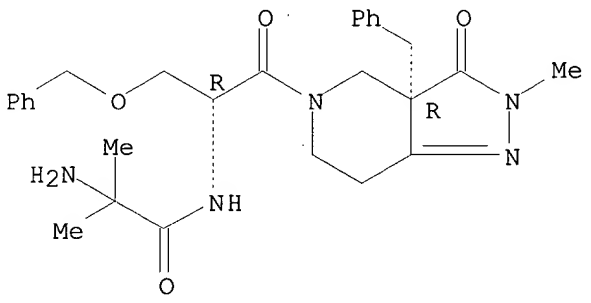
Absolute stereochemistry.



● HCl

RN 193273-66-4 USPATFULL
CN Propanamide, 2-amino-N-[(1R)-2-[(3aR)-2,3,3a,4,6,7-hexahydro-2-methyl-3-oxo-3a-(phenylmethyl)-5H-pyrazolo[4,3-c]pyridin-5-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

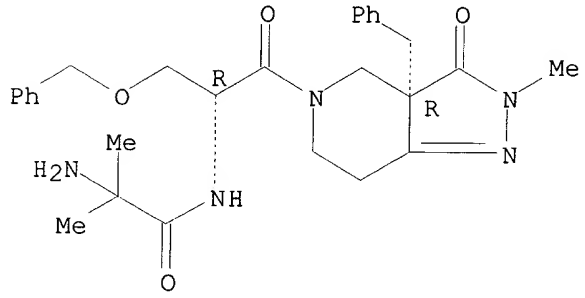


RN 193273-67-5 USPATFULL
CN Propanamide, 2-amino-N-[(1R)-2-[(3aR)-2,3,3a,4,6,7-hexahydro-2-methyl-3-oxo-3a-(phenylmethyl)-5H-pyrazolo[4,3-c]pyridin-5-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl-, monomethanesulfonate (9CI) (CA INDEX NAME)

CM 1

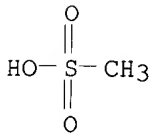
CRN 193273-66-4
CMF C28 H35 N5 O4

Absolute stereochemistry.



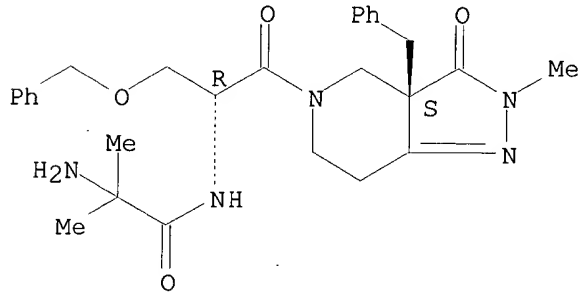
CM 2

CRN 75-75-2
CMF C H4 O3 S



RN 193273-68-6 USPATFULL
CN Propanamide, 2-amino-N-[(1R)-2-[(3aS)-2,3,3a,4,6,7-hexahydro-2-methyl-3-oxo-3a-(phenylmethyl)-5H-pyrazolo[4,3-c]pyridin-5-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



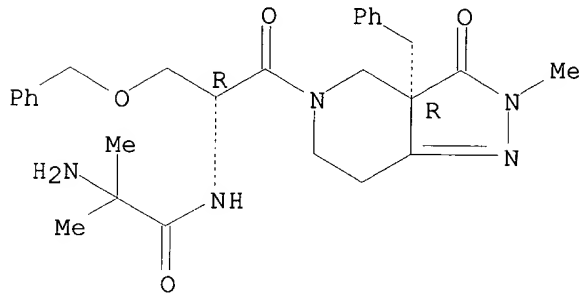
RN 193273-69-7 USPATFULL
CN Propanamide, 2-amino-N-[(1R)-2-[(3aR)-2,3,3a,4,6,7-hexahydro-2-methyl-3-oxo-3a-(phenylmethyl)-5H-pyrazolo[4,3-c]pyridin-5-yl]-2-oxo-1-

[(phenylmethoxy)methyl]ethyl]-2-methyl-, (2R,3R)-2,3-dihydroxybutanedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 193273-66-4
CMF C28 H35 N5 O4

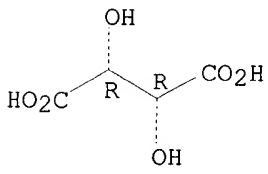
Absolute stereochemistry.



CM 2

CRN 87-69-4
CMF C4 H6 O6
CDES 1:R2:R*,R*

Absolute stereochemistry.



L73 ANSWER 2 OF 10 USPATFULL on STN
AN 2001:215078 USPATFULL
TI Combination therapy for **osteoporosis**
IN **Ke, Hua Zhu**, Ledyard, CT, United States
Thompson, David D., Gales Ferry, CT, United States
PA **Pfizer Inc.**, New York, NY, United States (U.S. corporation)
PI US 6323232 B1 20011127
WO 9731640 19970904
AI US 1998-117972 19980811 (9)
WO 1996-IB1462 19961223
19980811 PCT 371 date
19980811 PCT 102(e) date
PRAI US 1996-12412P 19960228 (60) <--
DT Utility
FS GRANTED
EXNAM Primary Examiner: Criares, Theodore J.
LREP Richardson, Peter C., Benson, Gregg C., Raymer, Gregory P.
CLMN Number of Claims: 2
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 2001
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Pharmaceutical combination compositions including certain estrogen agonists/antagonists and prostaglandins or prostaglandin agonists/antagonists. The compositions are useful for the treatment of **bone** disorders including **osteoporosis**.

TI Combination therapy for **osteoporosis**

IN **Ke, Hua Zhu**, Ledyard, CT, United States

IN **Thompson, David D.**, Gales Ferry, CT, United States

PA **Pfizer Inc.**, New York, NY, United States (U.S. corporation)

PRAI US 1996-12412P 19960228 (60) <--

AB Pharmaceutical combination compositions including certain estrogen agonists/antagonists and prostaglandins or prostaglandin agonists/antagonists. The compositions are useful for the treatment of **bone** disorders including **osteoporosis**.

SUMM This invention relates to a pharmaceutical combination of estrogen agonists/antagonists and agents that stimulate **bone** formation and increase **bone** mass, kits containing such combinations and the use of such combinations to treat conditions which present with low **bone** mass in mammals, including humans.

SUMM **Osteoporosis** is a systemic skeletal disease, characterized by low **bone** mass and deterioration of **bone** tissue, with a consequent increase in **bone** fragility and susceptibility to **fracture**. In the U.S., the condition affects more than 25 million people and causes more than 1.3 million **fractures** each year, including 500,000 spine, 250,000 hip and 240,000 wrist **fractures** annually. Hip **fractures** are the most serious, with 5-20% of patients dying within one year, and over 50% of survivors being incapacitated.

SUMM The elderly are at greatest risk of **osteoporosis**, and the problem is therefore predicted to increase significantly with the aging of the population. Worldwide **fracture** incidence is forecast to increase three-fold over the next 60 years, and one study estimates that there will be 4.5 million hip **fractures** worldwide in 2050.

SUMM Women are at greater risk of **osteoporosis** than men. Women experience a sharp acceleration of **bone** loss immediately following menopause. Other factors that increase **bone** loss leading to **osteoporosis** include smoking, alcohol abuse, a sedentary lifestyle and low calcium intake.

SUMM Estrogen is the agent of choice in preventing **osteoporosis** or post menopausal **bone** loss in women. In addition, Black, et al. in EP 0605193A1 report that estrogen, particularly when taken orally, lowers plasma. . . effects of estrogen. The significant undesirable side effects associated with estrogen therapy support the need to develop alternative therapies for **osteoporosis** that have the desirable beneficial effect on serum LDFL but do not cause undesirable side effects.

SUMM Recently, a number of estrogen agonists/antagonists have been proposed for treatment of **osteoporosis**. It has been reported (**Osteoporosis** conference Scrip No. 1812/13 Apr. 16/20, 1993, p. 29) that raloxifene, 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy) benzoyl]benzo[b] thiophene, mimics the favorable action of estrogen on **bone** and lipids but, unlike estrogen, has minimal uterine stimulatory effect. [Black, L. J. et al., Raloxifene (LY139481 Hcl) Prevents **Bone** Loss and Reduces Serum Cholesterol Without Causing Uterine Hypertrophy in Ovariectomized Rats, J. Clin. Invest., 1994, 93:63-69].

SUMM Also, tamoxifen, 1-(4-.beta.-dimethylaminoethoxyphenyl)-1,2-diphenyl-but-1-ene, is an antiestrogen that is proposed as an **osteoporosis** agent which has a pallative effect on breast cancer, but is reported to have some estrogenic activity in the uterus.. . .

SUMM . . . No. 5,254,594 (the disclosure of which is hereby incorporated by reference) discloses the use of droloxifene for the treatment of **bone** diseases including **osteoporosis**.

SUMM Agents such as droloxifene prevent **bone** loss and thereby

reduce the risk of **fracture** without estrogen's side effects. However, estrogen and estrogen agonists alone are only expected to reduce the **fracture** risk by about 50% leaving approximately 50% of ostepenic women still at risk for an **osteoporotic fracture**.

SUMM Non-estrogen agonists/antagonists such as bisphosphonates are also proposed for the treatment of **osteoporosis**. For example, Fosamax.RTM. is a bisphosphonate that is currently marketed for the treatment of **osteoporosis**. Other bisphosphonates currently undergoing regulatory review include risedronate, tiludronate, and ibandronate.

SUMM Frost et al. in "Treatment of **Osteoporosis** by Manipulation of Coherent **Bone** Cell Populations", Clinical Orthopedics and Related Research, 143, 227 (1979) discloses a theoretical model that suggests it should be possible to synchronize the activity and metabolism of **bone** cells by administering a **bone** cell activating agent first, followed by a **bone** resorption inhibiting agent and then normal **bone** formation is allowed to occur.

SUMM Tang et al., Restoring and Maintaining **Bone** in **Osteogenic** Female Rat Skeleton: I. Changes in **Bone** Mass and Structure, J. **Bone** Mineral Research 7 (9), p1093-1104, 1992 discloses data for the lose, restore and maintain (LRM) concept, a practical approach for reversing existing **osteoporosis**. The LRM concept uses anabolic agents to restore **bone** mass and architecture (+phase) and then switches to an agent with the established ability to maintain **bone** mass, to keep the new **bone** (+/- phase). The rat study utilized PGE.sub.2 and risedronate, a bisphosphonate, to show that most of the new cancellous and cortical **bone** induced by PGE.sub.2 can be maintained for at least 60 days after discontinuing PGE.sub.2 by administering risedronate.

SUMM Combinations of bisphosphonates and prostaglandins for the treatment of **osteoporosis** are disclosed. E.P. App. No. 0 381 296 teaches the use of a kit wherein a **bone** activating period or treatment regime is followed by a **bone** resorption inhibiting regime. Examples of **bone** activating compounds cited in this reference include parathyroid hormone (PTH), inorganic phosphate, growth hormone, fluoride, thyroid hormone (e.g., thyroxin), certain. . . vitamin D metabolites and prostaglandins (PGE.sub.2 in a dose regime of 10 mg/kg per day). Polyphosphonates are disclosed as the **bone** resorption inhibiting agents.

SUMM PCT/US93/08529 discloses the simultaneous delivery of a **bone** activating agent such as a prostaglandin that is chemically coupled to a **bone** resorption inhibiting compound which selectively delivers the **bone** activity agent to the target area. Upon gradual hyrolysis of the novel compound, the hydrolyzed products are able to provide **bone** resorption inhibiting activity (via the bisphosphonates) and **bone** growth or stimulating activity (via PGE.sub.2).

SUMM . . . E2 and risedronate (a bisphosphonate) was studied in Lin et al., Effects of Prostaglandin E2 and Risedronate Administration on Cancellous **Bone** in Older Female Rats, **Bone** 15 (5), p489-496, 1994.

SUMM . . . Monogr. Natl. Cancer Inst. (16), 161-167, 1994, states "The use of several nonestrogen approaches for the prevention and treatment of **osteoporosis** has been promising. Traditional recommendations to maintain skeletal integrity, such as weight-bearing exercise; a diet rich in calcium and limited. . .

SUMM Thus, although there exist a variety of **osteoporosis** therapies there is a continuing need and a continuing search in this field of art for alternative therapies due to only limited success of current therapies in reducing **osteoporotic fractures**.

SUMM . . . agonists/antagonists and anabolic agents and for the use of such compositions for the treatment of conditions which present with low **bone** mass, including **osteoporosis** in mammals (e.g., humans, particularly women).

SUMM Another aspect of this invention is a method for treating mammals which present with low **bone** mass comprising administering to a mammal having a condition which presents with low **bone** mass

SUMM A preferred aspect of this method is wherein the condition which presents with low **bone** mass is **osteoporosis**.

SUMM . . . compound alone and the amount of the second compound alone is insufficient to achieve the therapeutic effects of increase in **bone** formation and decrease in **bone** resorption if administered simultaneously and wherein the combined effect of the amounts of the first and second compounds is greater. . .

SUMM Yet another aspect of this invention is a synergistic method for treating mammals which present with low **bone** mass comprising administering to a mammal having a condition which presents with low **bone** mass

SUMM . . . compound alone and the amount of the second compound alone is insufficient to achieve the therapeutic effects of increase in **bone** formation and decrease in **bone** resorption if administered simultaneously and wherein the combined effect of the amounts of the first and second compounds is greater. . .

SUMM Another aspect of this invention is a kit containing a treatment for a condition which presents with low **bone** mass comprising:

SUMM Another aspect of this invention is directed to a method for treating mammals which present with low **bone** mass comprising administering to a mammal having a condition which presents with low **bone** mass

SUMM b. a therapeutically effective amount of a second compound, said second compound being sodium fluoride or N-[1(R)-[1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl) carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide: **MK-677**.

SUMM Another preferred aspect of this method is wherein the condition which presents with low **bone** mass is **osteoporosis**.

SUMM b. an amount of a second compound, said second compound being sodium fluoride or N-[1-(R)-[1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl) carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide:**MK-677**

SUMM . . . compound alone and the amount of the second compound alone is insufficient to achieve the therapeutic effects of increase in **bone** formation and decrease in **bone** resorption if administered simultaneously and wherein the combined effect of the amounts of the first and second compounds is greater. . .

SUMM Yet another aspect of this invention is a synergistic method for treating mammals which present with low **bone** mass comprising administering to a mammal having a condition which presents with low **bone** mass

SUMM b. an amount of a second compound, said second compound being sodium fluoride or N-[1-(R)-[1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl) carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide:**MK-677**

SUMM . . . compound alone and the amount of the second compound alone is insufficient to achieve the therapeutic effects of increase in **bone** formation and decrease in **bone** resorption if administered simultaneously and wherein the combined effect of the amounts of the first and second compounds is greater. . .

SUMM Another aspect of this invention is a kit containing a treatment for a condition which presents with low **bone** mass comprising:

SUMM b. a therapeutically effective amount of sodium fluoride or N-[1(R)-[1,2-Dihydro-1-methanesulfonylspiro [3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy) ethyl]-2-amino-2-methylpropanamide:

MK-677 and a pharmaceutically acceptable carrier in a second unit dosage form; and

SUMM Yet another aspect of this invention is a method for treating mammals which present with low **bone** mass comprising administering to a mammal having a condition which presents with low **bone** mass

SUMM A preferred aspect of this method is wherein the condition which presents with low **bone** mass is **osteoporosis**.

SUMM . . . compound alone and the amount of the second compound alone is insufficient to achieve the therapeutic effects of increase in **bone** formation and decrease in been resorption if administered simultaneously and wherein the combined effect of the amounts of the first. . .

SUMM Yet another aspect of this invention is a synergistic method for treating mammals which present with low **bone** mass comprising administering to a mammal having a condition which presents with low **bone** mass

SUMM . . . compound alone and the amount of the second compound alone is insufficient to achieve the therapeutic effects of increase in **bone** formation and decrease in **bone** resorption if administered simultaneously and wherein the combined effect of the amounts of the first and second compounds is greater. . .

SUMM Yet another aspect of this invention is a kit containing a treatment for a condition which presents with low **bone** mass comprising:

SUMM . . . art will recognize that other anti-resorptive agents (bisphosphonate, estrogen, estradiol, premarin, estrone, estriol or 17.alpha.- or 17.beta.-ethynyl estradiol) and other **bone** anabolic agents (androgen, androgen agonist/antagonist) may be used together or with any of the agents described herein in this invention. . .

SUMM For example, the anti-resorptive agent droloxifene may be combined with an individual **bone** anabolic agent such as parathyroid hormone, growth hormone or growth hormone secretagogues.

SUMM The phrase "condition which presents with low **bone** mass" refers to a condition where the level of **bone** mass is below the age specific normal as defined in standards by the World Health Organization "Assessment of **Fracture** Risk and its Application to Screening for Postmenopausal **Osteoporosis** (1994), Report of a World Health Organization study Group. World Health Organization Technical Series 843". Childhood idiopathic and primary **osteoporosis** are also included. Included in the treatment of **osteoporosis** is the prevention or attenuation of long term complications such as curvature of the spine, loss of height, prosthetic surgery, and prevention of prostate malfunctioning. Also included is increasing the **bone fracture** healing rate and enhancing the rate of successful **bone** grafts. Also included is periodontal disease and alveolar **bone** loss.

SUMM The phrase "condition which presents with low **bone** mass" also refers to a mammal known to have a significantly higher than average chance of developing such diseases as are described above including **osteoporosis** (e.g., post-menopausal women, men over the age of 60, and persons being treated with drugs known to cause **osteoporosis** as a side effect (such as glucocorticoid)).

SUMM Those skilled in the art will recognize that the term **bone** mass actually refers to **bone** mass per unit area which is sometimes (although not strictly correctly) referred to a **bone** mineral density.

SUMM The pharmaceutical compositions of this invention result in a more rapid and higher magnitude **bone** mass gain than is achievable with the same doses of estrogen agonists/antagonists as described above alone or an agent which stimulates an increase in **bone** mineral density as described above alone. Thus, these combinations have a synergistic action, increasing **bone** mass and decreasing **fracture** rates to a greater extent than is achievable through

use of either agent alone. This invention makes a significant contribution to the art by providing compositions and methods that increase and maintain **bone** mass resulting in prevention, retardation, and/or regression of **osteoporosis** and related **bone** disorders.

SUMM . . . the first compound of this invention. The term estrogen agonist/antagonist refers to compounds which bind with the estrogen receptor, inhibit **bone** turnover and prevent **bone** loss. Such activities are readily determined by those skilled in the art according to standard assays including estrogen receptor binding assays (see In Vitro Estrogen Receptor Binding Assay hereinafter), standard **bone** histomorphometric and densitometer methods (see Estrogen Agonist/Antagonist Protocol hereinafter, and Eriksen E. F. et al., **Bone** Histomorphometry, Raven Press, New York, 1994, pages 1-74; Grier S. J. et. al., The Use of Dual-Energy X-Ray Absorptiometry In Animals, Inv. Radiol., 1996, 31(1):50-62; Wahner H. W. and Fogelman I., The Evaluation of **Osteoporosis**:Dual Energy X-Ray Absorptiometry in Clinical Practice., Martin Dunitz Ltd., London 1994, pages 1-296). A variety of these compounds are described. . .

SUMM The second compound of this invention may be any compound as described below that augments **bone** mass to a level which is above the **bone fracture** threshold (as detailed in the World Health Organization Study World Health Organization, "Assessment of **Fracture** Risk and its Application to Screening for Postmenopausal **Osteoporosis** (1994). Report of a WHO Study Group. World Health Organization Technical Series 843").

SUMM . . . which are analogs of the natural prostaglandins PGD.sub.1, PGD.sub.2, PGE.sub.2, and PGF.sub.2 .alpha. which are useful in the treatment of **osteoporosis**. These compounds bind to the prostaglandin receptors. Such binding is readily determined by those skilled in the art according to. . .

SUMM Norrdin et al., The Role of Prostaglandins in **Bone** in Vivo, Prostaglandins Leukotriene Essential Fatty Acids 41, 139-150, 1990 is a review of **bone** active prostaglandins.

SUMM . . . Prostaglandin E.sub.2, Biochemical and Biophysical Research Communications, 1993, 197(1): 263-270) and mimic the action of prostaglandin in vivo (e.g., stimulate **bone** formation and increase **bone** mass). Such actions are readily determined by those skilled in the art according to standard assays (e.g., see Anabolic Agent Protocol described hereinafter and Eriksen E.f. et al., **Bone** Histomorphometry, Raven Press, New York, 1994, pages 1-74; Grier S. J. et. al., The Use of Dual-Energy X-Ray Absorptiometry in. . .

SUMM Commonly assigned U.S. Pat. No. 3,932,389 (the disclosure of which is hereby incorporated by reference) discloses 2-descarboxy-2-(tetrazol-5yl)-11-desoxy-15-substituted-omega-pentanorprostaglandins useful for **bone** formation activity.

SUMM . . . assigned U.S. Pat. No. 4,018,892 (the disclosure of which is hereby incorporated by reference) discloses 16-aryl-13,14-dihydro-PGE.sub.2 p-biphenyl esters useful for **bone** formation activity.

SUMM Commonly assigned U.S. Pat. No. 4,219,483 (the disclosure of which is hereby incorporated by reference) disclosures 2,3,6-substituted-4-pyrones useful for **bone** formation activity.

SUMM Commonly assigned U.S. Pat. No. 4,132,847 (the disclosure of which is hereby incorporated by reference) discloses 2,3,6-substituted-4-pyrones useful for **bone** formation activity.

SUMM U.S. Pat. No. 4,000,309 (the disclosure of which is hereby incorporated by reference) disclosures 16-aryl-13,14-dihydro-PGE.sub.2 p-biphenyl esters useful for **bone** formation activity.

SUMM U.S. Pat. No. 3,982,016 (the disclosure of which is hereby incorporated by reference) discloses 16-arly-13,14-dihydro-PGE.sub.2 p-biphenyl esters useful for **bone** formation activity.

SUMM U.S. Pat. No. 4,621,100 (the disclosure of which is hereby incorporated by reference) discloses substituted cyclopentanes useful for **bone** formation activity.

SUMM U.S. Pat. No. 5,216,183 (the disclosure of which is hereby incorporated by reference) discloses cyclopentanoenes useful for **bone** formation activity.

SUMM . . . in the art according to biological protocols (e.g., see Anabolic Agent Protocol described hereinafter and Eriksen E. F. et al., **Bone** Histomorphometry, Raven Press, New York, 1994, pages 1-74; Grier S. J. et. al., The Use of Dual-Energy X-Ray Absorptiometry in. . .

SUMM . . . invention. The term parathyroid hormone refers to parathyroid hormone, fragments or metabolites thereof and structural analogs thereof which can stimulate **bone** formation and increase **bone** mass. Such functional activity is readily determined by those skilled in the art according to standard assays (e.g., see Anabolic Agent Protocol described hereinafter and Eriksen E. F. et al., **Bone** Histomorphometry, Raven Press, New York, 1994, pages 1-74; Grier S. J. et. al., The Use of Dual-Energy X-Ray Absorptiometry In. . .

SUMM "Human Parathyroid Peptide Treatment of Vertebral **Osteoporosis** ", Osteporosis Int., 3, (Supp 1):199-203.

SUMM "PTH 1-34 Treatment of **Osteoporosis** with Added Hormone Replacement Therapy: Biochemical, Kinetic and Histological Responses" Osteporosis Int. 1:162-170.

SUMM . . . secretagogue refers to compounds which stimulate the release of growth hormone or mimic the action of growth hormone (e.g., increase **bone** formation leading to increased **bone** mass). Such actions are readily determined by those skilled in the art according to standard assays (e.g., as described hereinafter).. . .

SUMM In particular a preferred growth hormone secretagogue is N-[1(R)-[1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide: **MK-677**.

SUMM The pharmaceutical combinations and methods of this invention are all adapted to therapeutic use as agents that either activate **bone** turnover or prevent **bone** resorption or increase **bone** formation in mammals, particularly humans. Since these functions are closely related to the development of **osteoporosis** and **bone** related disorders, these combinations, by virtue of their action on **bone**, prevent, arrest, regress or reverse **osteoporosis**.

SUMM . . . utility of the compounds of the present invention as medical agents in the treatment of conditions which present with low **bone** mass (e.g., **osteoporosis**) in mammals (e.g. humans, particularly the female) is demonstrated by the activity of the compounds of this invention in conventional. . .

SUMM . . . months). In the castrated rats, treatment can be started at the next day after surgery (for the purpose of preventing **bone** loss) or at the time **bone** loss has already occurred (for the purpose of restoring **bone** mass).

SUMM The following protocols are described as using PGE2 as the **bone** anabolic agent and droloxifene as the antiresorptive agent, however, other anabolic agents and antiresorptive agents may be tested in the. . .

SUMM . . . sham-operated or ovariectomized (OVX) at month 0. Three months post-surgery, OVX rats receive either Prostaglandin E.sub.2 (PGE.sub.2), a known anabolic **bone** agent, at 3 mg/kg/day (subcutaneously injection), or PGE.sub.2 at 3 mg/kg/day (subcutaneously injection) combined with droloxifene (DRO) at 10 mg/kg/day. . .

SUMM . . . Droloxifene solution is given daily p.o. at 1 ml/rat. All rats are given subcutaneous injections of 10 mg/kg kalcein (flurochrome **bone** marker, Sigma Chemical Co. St. Louis Mo.) twelve and two days before death to examine the dynamic changes in **bone**

tissues.

SUMM Femoral **Bone** Mineral Measurements: The right femur from each rat is removed at autopsy and scanned using dual energy x-ray absorptiometry (DXA,. . . is 5.08.times.1.902 cm, resolution is 0.0254.times.0.0127 cm and scan speed is 7.25 mm/second. The femoral scan images are analyzed and **bone** area, **bone** mineral content (BMC), and **bone** mineral density (BMD) of whole femora (WF), distal femoral metaphyses (SFM), femoral shaft (FS), and proximal femora (PF) are determined.

SUMM Lumbar Vertebral **Bone** Mineral Measurements: Dual energy x-ray absorptimoetry (QDR 1000/W, Hologic, Inc. Waltham, Mass.) equipped with a "Regional High Resolution Scan" software (Hologic, Inc., Walthmam, Mass.) is used to determined the **bone** area, **bone** mineral content (BMC), and **bone** mineral density (BMD) of whole lumbar spine and each of the six lumbar vertebrae (LV1-6) in the anesthetized rats. The. . . resolution is 0/0254.times.0.0127 cm, and scan speed is 7.25 mm/sec. The whole lumbar spine scan image is obtained and analyzed. **Bone** area (BA), and **bone** mineral content (BMC) is determined, and **bone** mineral density is calculated (MBC divided by BA) for the whole lumbar spine and each of the six lumbar vertebrae. . .

SUMM Proximal Tibial Metaphyseal Cancellous **Bone** Histomorphometric Analyses: The right tibia is removed at autopsy, dissected free of muscle, and cut into three parts. The proximal. . . using Reichert-Jung Polycut S microtome. One 4 .mu.m and one 10 .mu.m sections from each rat is used for cancellous **bone** histomorphometry. The 4 .mu.m sections is stained with modified Masson's Trichrome stain while the 10 .mu.m sections remained unstained.

SUMM . . . in order to restrict measurements to the secondary spongiosa. The 4 .mu.m sections are used to determine indices related to **bone** volume, **bone** structure, and **bone** resorption, while the 10 .mu.m sections are used to determine indices related to **bone** formation and **bone** turnover.

SUMM I. Measurements and calculations related to trabecular **bone** volume and structure:

SUMM 2. Trabecular **bone** area (BV, mm.sup.2): total area of trabeculae within TV.

SUMM 3. Trabecular **bone** perimeter (BS, mm): the length of total perimeter of trabeculae.

SUMM 4. Trabecular **bone** volume (BV/TV, %): BV/TV.times.100.

SUMM 5. Trabecular **bone** number (TBN, #/mm): 1.199/2.times.BS/TV.

SUMM 6. Trabecular **bone** thickness (TBT, .mu.m): (2000/1.199).times.(BV/BS).

SUMM 7. Trabecular **bone** separation (TBS, .mu.m): (2000.times.1.199).times.(TV-BV).

SUMM II. Measurements and calculations related to **bone** resorption:

SUMM 1. **Osteoclast** number (OCN, #): total number of **osteoclast** within total metaphyseal area.

SUMM 2. **Osteoclast** perimeter (OCP, mm): length of trabecular perimeter covered by **osteoclast**.

SUMM 3. **Osteoclast** number/mm (OCN/mm, #/mm): OCN/BS.

SUMM 4. Percent **osteoclast** perimeter (% OCP, %): OCP/BS.times.100.

SUMM III. Measurements and calculations related to **bone** formation and turnover:

SUMM 6. **Bone** formation rate/surface ref. (BFR/BS, .mu.m.sup.2 /d/.mu.m): (SLS/2+DLS).times.MAR/BS.

SUMM 7. **Bone** turnover rate (BTR, %/y): (SLS/2+DLS).times.MAR/BV.times.100.

SUMM Estrogen agonist/antagonists are a class of compounds which inhibits **bone** turnover and prevents estrogen-deficiency induced **bone** loss. The ovariectomized rat **bone** loss model has been widely used as a model of postmenopausal **bone** loss. Using this method, one can test the efficacy of the estrogen

agonist/antagonist compounds in preventing **bone** loss and inhibiting **bone** resorption.

SUMM . . . p.o.) for a certain period (such as 4 weeks). All rats are given subcutaneous injections of 10 mg/kg calcein (fluorochrome **bone** marker) 12 and 2 days before being sacrificed in order to examine the dynamic changes in **bone** tissue. After 4 weeks of treatment, the rats are autopsied. The following endpoints are determined:

SUMM Femoral **Bone** Mineral Measurements: The right femur from each rat is removed at autopsy and scanned using dual energy x-ray absorptiometry (DEXA,. . . is 5.08.times.1.902 cm, resolution is 0.0254.times.0.0127 cm and scan speed is 7.25 mm/second. The femoral scan images are analyzed and **bone** area, **bone** mineral content (BMC), and **bone** mineral density (BMD) of whole femora (WF), distal femoral metaphyses (DFM), femoral shaft (FS), and proximal femora (PF) is determined.

SUMM Proximal Tibial Metaphyseal Cancellous **Bone** Histomorphometric Analyses: The right tibia is removed at autopsy, dissected free of muscle, and cut into three parts. The proximal. . . using Reichert-Jung Polycut S microtome. One 4 .mu.m and one 10 .mu.m sections from each rat are used for cancellous **bone** histomorphometry. The 4 .mu.m sections are stained with modified Masson's Trichrome stain while the 10 .mu.m sections remained unstained.

SUMM . . . in order to restrict measurements to the secondary spongiosa. The 4 .mu.m sections are used to determine indices related to **bone** volume, **bone** structure, and **bone** resorption, while the 10 .mu.m sections are used to determine indices related to **bone** formation and **bone** turnover.

SUMM I. Measurements and calculations related to trabecular **bone** volume and structure:

SUMM 2. Trabecular **bone** area (BV, mm.sup.2): total area of trabeculae within TV.

SUMM 3. Trabecular **bone** perimeter (BS, mm): the length of total perimeter of trabeculae.

SUMM 4. Trabecular **bone** volume (BV/TV, %): BV/TV.times.100.

SUMM 5. Trabecular **bone** number (TBN, #/mm): 1.199/2.times.BS/TV.

SUMM 6. Trabecular **bone** thickness (TBT, .mu.m): (200/1.199).times.(BV/BS).

SUMM 7. Trabecular **bone** separation (TBS, .mu.m): (2000.times.1.199).times.(TV-BV).

SUMM II. Measurements and calculations related to **bone** resorption:

SUMM 1. **Osteoclast** number (OCN, #): total number of **osteoclast** within total metaphyseal area.

SUMM 2. **Osteoclast** perimeter (OCP, mm): length of trabecular perimeter covered by **osteoclast**.

SUMM 3. **Osteoclast** number/mm (OCN/mm, #/mm): OCN/BS.

SUMM 4. Percent **osteoclast** perimeter (% OCP, %): OCP/BS.times.100.

SUMM III. Measurements and calculations related to **bone** formation and turnover:

SUMM 6. **Bone** formation rate/surface ref. (BFR/BS, .mu.m.sup.2 /d/.mu.m): (SLS/2+DLS).times.MAR/BS.

SUMM 7. **Bone** turnover rate (BTR, %/y): (SLS/2+DLS).times.MAR/BV.times.100.

SUMM The activity of anabolic **bone** agents in stimulating **bone** formation and increasing **bone** mass can be tested in intact male or female rats, sex hormone deficient male (orchidectomy) or female (ovariectomy) rats.

SUMM . . . 2 months). In the castrated rats, treatment is started at the next day after surgery (for the purpose of preventing **bone** loss) or at the time **bone** loss has already occurred (for the purpose of restoring **bone** mass). During the study, all rats are allowed free access to water and a pelleted commercial diet (Teklad Rodent Diet. . .

SUMM Femoral **Bone** Mineral Measurements: The right femur from each rat is removed at autopsy and scanned using dual energy x-ray absorptiometry (DEXA,. . . is 5.08.times.1.902 cm, resolution is 0.0254.times.0.0127 cm and scan speed is 7.25 mm/second. The femoral scan images are analyzed and **bone** area, **bone** mineral content (BMC), and **bone** mineral density (BMD) of whole femora (WF), distal femoral metaphyses (DFM), femoral shaft (FS), and proximal femora (PF) are determined

SUMM Proximal Tibial Metaphyseal Cancellous **Bone** Histomorphometric Analyses: The right tibia is removed at autopsy, dissected free of muscle, and cut into three parts. The proximal. . . using Reichert-Jung Polycut S microtome. One 4 .mu.m and one 10 .mu.m sections from each rat are used for cancellous **bone** histomorphometry. The 4 .mu.m sections are stained with modified Masson's Trichrome stain while the 10 .mu.m sections remained unstained.

SUMM . . . in order to restrict measurements to the secondary spongiosa. The 4 .mu.m sections are used to determine indices related to **bone** volume, **bone** structure, and **bone** resorption, while the 10 .mu.m sections are used to determine indices related to **bone** formation and **bone** turnover.

SUMM I. Measurements and calculations related to trabecular **bone** volume and structure:

SUMM 2. Trabecular **bone** area (BV, mm.sup.2): total area of trabeculae within TV.

SUMM 3. Trabecular **bone** perimeter (BS, mm): the length of total perimeter of trabeculae.

SUMM 4. Trabecular **bone** volume (BV/TV, %): BV/TV.times.100.

SUMM 5. Trabecular **bone** number (TBN, #/mm): 1.199.times.2.times.BS/TV.

SUMM 6. Trabecular **bone** thickness (TBT, .mu.m): 2000/1.199).times.(BV/BS).

SUMM 7. Trabecular **bone** separation (TBS, .mu.m): (2000.times.1.199).times.(TV-BV).

SUMM II. Measurements and calculations related to **bone** resorption:

SUMM 1. **Osteoclast** number (OCN, #): total number of **osteoclast** within total metaphyseal area.

SUMM 2. **Osteoclast** perimeter (OCP, mm): length of trabecular perimeter covered by **osteoclast**.

SUMM 3. **Osteoclast** number/mm (OCN/mm, #/mm): OCN/BS.

SUMM 4. Percent **osteoclast** perimeter (% OCP, %): OCP/BS.times.100.

SUMM III. Measurements and calculations related to **bone** formation and turnover:

SUMM 6. **Bone** formation rate/surface ref. (BFR/BS, .mu.m.sup.2 /d/.mu.m): (SLS/2+DLS).times.MAR/BS.

SUMM 7. **Bone** turnover rate (BTR, %/y): (SLS/2+DLS).times.MAR/BV.times.100.

SUMM For example, the **bone** anabolic agent can be used alone or in combination with an anti-resorptive agent for three months to three years, followed. . . agent alone for three months to three years, with optional repeat of the full treatment cycle. Alternatively, for example, the **bone** anabolic agent can be used alone or in combination with an anti-resorptive agent for three months to three years, followed. . . second compound as described above (e.g., PGE.sub.2) may be administered once daily for a period of time sufficient to augment **bone** mass to a level which is above the **bone fracture** threshold (World Health Organization "Assessment of **Fracture** Risk and its Application to Screening for Postmenopausal **Osteoporosis** (1994). Report of a World Health Organization Study Group. World Health Organization Technical Series 843") followed by administration of a. . .

SUMM . . . dosages given below are a guideline and the physician may titrate doses of the drug to achieve the activity (e.g., **bone** mass augmentation) that the physician considers appropriate for the

individual patient. In considering the degree of activity desired, the physician must balance a variety of factors such as **bone** mass starting level, age of the patient, presence of preexisting disease, as well as presence of other diseases (e.g., cardiovascular).. . .

SUMM The amount of the anti-resorptive agent to be used is determined by its activity as a **bone** loss inhibiting agent. This activity is determined by means of an individual compound's pharmacokinetics and its minimal maximal effective dose in inhibition of **bone** loss using a protocol as described above (ESTROGEN AGONIST/ANTAGONIST PROTOCOL).

SUMM In general an effective dosage for the activities of this invention, for example the **bone** resorption activities of this invention, for the first compounds of this invention is in the range of 0.01 to 200. . .

SUMM In general an amount of a **bone** anabolic agent (e.g., PGE.sub.2) is used that is sufficient to augment **bone** mass to a level which is above the **bone fracture** threshold (as detailed in the World Health Organization Study previously cited herein).

SUMM In general an effective dosage for the **bone** anabolic agent described above is in the range of 0.001 to 100 mg/kg/day, preferably 0.1 to 10 mg/kg/day.

SUMM Since the present invention relates to the augmentation and maintenance of **bone** mass by treatment with a combination of active ingredients which may be administered separately, the invention also relates to combining. . .

SUMM . . . tablet or capsule or several pills or capsules to be taken on a given day. Also a daily dose of **bone** anabolic agent can consist of one tablet or capsule while a daily dose of a anti-resorptive agent can consist of. . .

DETD . . . ovariectomized (OVX) at month 0. Three months post-surgery, OVX rats were treated with either Prostaglandin E.sub.2 (PGE.sub.2), a known anabolic **bone** agent, at 3 mg/kg/day (subcutaneously injection), or PGE.sub.2 at 3 mg/kg/day (subcutaneously injection) combined with droloxifene (DRO) at 10 mg/kg/day. . .

DETD Lumbar Vertebral **Bone** Mineral Measurements

DETD . . . Inc., Waltham, Mass.) equipped with a "Regional High Resolution Scan" software (Hologic, Inc., Waltham, Mass.) was used to determined the **bone** area, **bone** mineral content (BMC), and **bone** mineral density (BMD) of whole lumbar spine and each of the six lumbar vertebrae (LV1-6) in the anesthetized rats. The. . . resolution was 0.0254.times.0.0127 cm, and scan speed was 7.25 mm/sec. The whole lumbar spine scan image was obtained and analyzed. **Bone** area (BA), and **bone** mineral content (BMC) were determined, and **bone** mineral density was calculated (MBC divided by BA) for the whole lumbar spine and each of the six lumbar vertebrae. . .

DETD . . . On the other hand, when DRO treatment was given to these OVX rats after discontinuation of PGE.sub.2, the PGE.sub.2 -restored **bone** was completely maintained. Similarly, discontinuation of both PGE.sub.2 and DRO for 1.5 months produced a significant decrease in BMD of LV3. However, when PGE.sub.2 was withdrawn and DRO treatment was continued for another 1.5 months, no **bone** loss was found in the lumbar spine of these OVX rats. We concluded that DRO, an anti-resorptive agent, did not blunt the anabolic effects of PGE.sub.2 in **osteogenic** rats. Further, DRO was efficacious in maintaining PGE.sub.2 -restored **bone** after discontinuation of PGE.sub.2. These data support the strategy of using an anabolic agent to restore **bone** mass in the **osteoporotic** skeleton followed by an anti-resorptive agent to maintain the restored **bone** mass.

CLM What is claimed is:

2. A method for treating a mammal having a condition which presents with

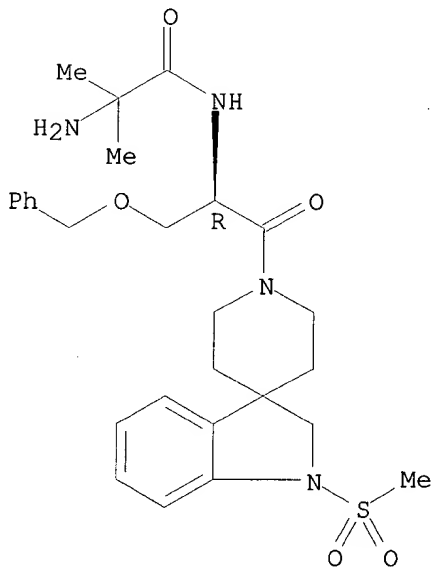
low **bone** mass, said method comprising administering to said mammal a pharmaceutical composition comprising synergistic effective amounts of lasofoxifene and PGE2 in. . .

IT **Bone, disease**
IT **Bone formation**
IT Drug delivery systems
IT **Osteoporosis**
(estrogen agonists/antagonists and prostaglandins or prostaglandin agonists/antagonists as combination therapy for bone disorders including osteoporosis)
IT **Bone**
(resorption, inhibitors; estrogen agonists/antagonists and prostaglandins or prostaglandin agonists/antagonists as combination therapy for bone disorders including osteoporosis)
IT 363-24-6, PGE2 551-11-1, PGF2.alpha. 745-65-3, PGE1 7681-49-4, Sodium fluoride, biological studies 9002-64-6, Parathyroid hormone 10540-29-1, Tamoxifen 17968-82-0, PGD1 31477-60-8, Centchroman 41598-07-6, PGD2 68047-06-3, 4-Hydroxytamoxifen 82413-20-5, Droloxifene 84449-90-1, Raloxifene 116057-75-1, Idoxifene 123123-44-4 **159752-10-0**, MK-677 180915-78-0 180915-84-8 180915-86-0 180916-14-7 180916-15-8 180916-16-9 193274-89-4 195962-24-4
(estrogen agonists/antagonists and prostaglandins or prostaglandin agonists/antagonists as combination therapy for bone disorders including osteoporosis)
IT **159752-10-0**, MK-677
(estrogen agonists/antagonists and prostaglandins or prostaglandin agonists/antagonists as combination therapy for bone disorders including osteoporosis)
RN 159752-10-0 USPATFULL
CN Propanamide, 2-amino-N-[(1R)-2-[1,2-dihydro-1-(methylsulfonyl)spiro[3H-indole-3,4'-piperidin]-1'-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl-, monomethanesulfonate (9CI) (CA INDEX NAME)

CM 1

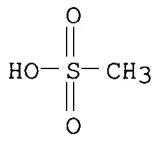
CRN 159634-47-6
CMF C27 H36 N4 O5 S
CDES 1:R

Absolute stereochemistry.



CM 2

CRN 75-75-2
CMF C H4 O3 S



L73 ANSWER 3 OF 10 USPATFULL on STN
AN 2001:197037 USPATFULL
TI Method of treatment using certain growth-hormone secret agogues
IN Carpino, Philip A, Groton, CT, United States
DaSilva-Jardine, Paul A, Providence, RI, United States
Lefker, Bruce A, Gales Ferry, CT, United States
Ragan, John A, Gales Ferry, CT, United States
PA **Pfizer Inc**., New York, NY, United States (U.S. corporation)
PI US 6313140 B1 20011106
AI US 2000-593581 20000613 (9)
RLI Continuation of Ser. No. US 1999-259691, filed on 1 Mar 1999, now patented, Pat. No. US 6107306 Division of Ser. No. US 1998-68566, filed on 21 May 1998, now abandoned Continuation of Ser. No. WO 1996-IB1353, filed on 4 Dec 1996
PRAI US 1995-9469P 19951228 (60) <--
DT Utility
FS GRANTED
EXNAM Primary Examiner: Dentz, Bernard
LREP Richardson, Peter C., Benson, Gregg C., Ronau, Robert T.
CLMN Number of Claims: 10
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 4200
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention is directed to compounds of the formula ##STR1##

and the pharmaceutically-acceptable salts thereof, where the substituents are as defined in the Specification, which are growth hormone secretogogues and which increase the level of endogenous growth hormone. The compounds of this invention are useful for the treatment and prevention of **osteoporosis**, congestive heart failure, frailty associated with aging, obesity; accelerating **bone fracture** repair, attenuating protein catabolic response after a major operation, reducing cachexia and protein loss due to chronic illness, accelerating wound healing, or accelerating the recovery of burn patients or patients having undergone major surgery; improving muscle strength, mobility, maintenance of skin thickness, metabolic homeostasis or renal homeostasis. The compounds of the present invention are also useful in treating **osteoporosis** when used in combination with: a bisphosphonate compound such as alendronate; estrogen, premarin, and optionally progesterone; an estrogen agonist or antagonist; or calcitonin, and pharmaceutical compositions useful therefor. Further, the present invention is directed to pharmaceutical compositions useful for increasing the endogenous production or release of growth hormone in a human or other animal which comprises an effective amount of a compound of the present invention and a growth hormone secretagogue selected from GHRP-6, Hexarelin, GHRP-1, growth

hormone releasing factor (GRF), IGF-1, IGF-2 or B-HT920. The invention is also directed to intermediates useful in the preparation of compounds of formula I.

PA **Pfizer Inc.**, New York, NY, United States (U.S. corporation)

PRAI US 1995-9469P 19951228 (60) <--

AB . . . increase the level of endogenous growth hormone. The compounds of this invention are useful for the treatment and prevention of **osteoporosis**, congestive heart failure, frailty associated with aging, obesity; accelerating **bone fracture** repair, attenuating protein catabolic response after a major operation, reducing cachexia and protein loss due to chronic illness, accelerating wound. . . maintenance of skin thickness, metabolic homeostasis or renal homeostasis. The compounds of the present invention are also useful in treating **osteoporosis** when used in combination with: a bisphosphonate compound such as alendronate; estrogen, premarin, and optionally progesterone; an estrogen agonist or. . .

SUMM This invention relates to dipeptide compounds which are growth hormone secretagogues and are useful for the treatment and prevention of **osteoporosis**.

SUMM . . . the truncal region. Decreased skeletal and cardiac muscle mass and muscle strength lead to a significant reduction in exercise capacity. **Bone** density is also reduced. Administration of exogenous growth hormone has been shown to reverse many of the metabolic changes. Additional. . .

SUMM The compounds of WO 94/11012 and WO 94/13696 are reported to be useful in the treatment of **osteoporosis** in combination with parathyroid hormone or a bisphosphonate.

SUMM a method for the treatment or prevention of **osteoporosis** which comprises administering to a human or other animal in need of such treatment or prevention an amount of a compound of Formula I which is effective in treating or preventing **osteoporosis**;

SUMM a method for the treatment or prevention of **osteoporosis** which comprises administering to a human or other animal with **osteoporosis** a combination of a bisphosphonate compound such as alendronate, and especially preferred is the bisphosphonate compound ibandronate, and a compound. . .

SUMM a method for the treatment or prevention of **osteoporosis** which comprises administering to a human or other animal with **osteoporosis** a combination of estrogen or Premarin.RTM. and a compound of Formula I and optionally progesterone;

SUMM a method for the treatment of **osteoporosis** which comprises administering to a human or other animal with **osteoporosis** a combination of an estrogen agonist or antagonist such as tamoxifen, droloxifene, raloxifene and idoxifene and a compound of Formula. . .

SUMM a particularly preferred method for the treatment of **osteoporosis** comprises administering to a human or other animal with **osteoporosis** a combination of an estrogen agonist or antagonist such as Cis-6-(4-fluoro-phenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol;

SUMM a method for the treatment of **osteoporosis** which comprises administering to a human or other animal with **osteoporosis** a combination of calcitonin and a compound of Formula I;

SUMM In another aspect, this invention provides methods for accelerating **bone fracture** repair, attenuating protein catabolic response after a major operation, reducing cachexia and protein loss due to chronic illness such as. . . effective in promoting release of endogenous growth hormone; of the instant method a preferred method of use is to accelerate **bone fracture** repair or for accelerating the recovery of patients having undergone major surgery.

SUMM . . . efficiency of animals raised for meat production to improve carcass quality; to increase milk production in dairy cattle; improvement of **bone** or wound healing and improvement in vital organ function. The compounds of the present invention by inducing

endogenous GH secretion. . .

SUMM . . . Formula I or another compound which exhibits a different activity, e.g., an antibiotic growth permittant or an agent to treat **osteoporosis** or with other pharmaceutically active materials wherein the combination enhances efficacy and minimizes side effects.

SUMM . . . follows: stimulating growth hormone release in elderly humans; treating growth hormone deficient adufts: preventing catabolic side effects of glucocorticoids, treating **osteoporosis**, stimulating the immune system, acceleration of wound healing, accelerating **bone fracture** repair, treating growth retardation, treating congestive heart failure as disclosed in PCT publications WO 95128173 and WO 95/28174 (an example. . . as gastrointestinal surgery; treating intrauterine growth retardation, skeletal dysplasia, hypercortisonism and Cushings syndrome; replacing growth hormone in stressed patients; treating **osteochondrodysplasias**, Noonans syndrome, sleep disorders, Alzheimer's disease, delayed wound healing, and psychosocial deprivation; treating of pulmonary dysfunction and ventilator dependency; attenuating. . . improving muscle strength, increasing muscle mass, mobility, maintenance of skin thickness, metabolic homeostasis, renal hemeostasis in the frail elderly; stimulating **osteoblasts**, **bone** remodelling, and cartilage growth; treating neurological diseases such as peripheral and drug induced neuropathy, Guillian-Barre Syndrome, amyotrophic lateral sclerosis, multiple. . .

SUMM . . . one times the dose levels which are effective when these compounds and secretagogues are used singly. Combined therapy to inhibit **bone** resorption, prevent **osteoporosis**, reduce skeletal **fracture**, enhance the healing of **bone fractures**, stimulate **bone** formation and increase **bone** mineral density can be effectuated by combinations of bisphosphonates and the growth hormone secretagogues of this invention, see PCT publication. . . of bisphosphonates for these utilities has been reviewed, for example, by Hamdy, N. A. T., Role of Bisphosphonates in Metabolic **Bone** Diseases, Trends In Endocrinol. Metab., 1993, 4, pages 19-25. Bisphosphonates with these utilities include but are not limited to alendronate,. . . invention of between 0.01 mg/kg to 20 mg/kg of body weight are administered to patients to obtain effective treatment of **osteoporosis**.

SUMM . . . the second compound of this invention. The term estrogen agonist/antagonist refers to compounds which bind with the estrogen receptor, inhibit **bone** turnover and prevent **bone** loss. In particular, estrogen agonists are herein defined as chemical compounds capable of binding to the estrogen receptor sites in. . . activities are readily determined by those skilled in the art according to standard assays including estrogen receptor binding assays, standard **bone** histomorphometric and densitometer methods (see Eriksen E. F. et al., **Bone** Histomorphometry, Raven Press, New York, 1994, pages 1-74; Grier S. J. et. al., The Use of Dual-Energy X-Ray Absorptiometry In Animals, Inv. Radiol., 1996, 31(1):50-62; Wahner H. W. and Fogelman I., The Evaluation of **Osteoporosis**: Dual Energy X-Ray Absorptiometry in Clinical Practice., Martin Dunitz Ltd., London 1994, pages 1-296). A variety of these compounds are. . .

SUMM The amount of the anti-resorptive agent to be used is determined by its activity as a **bone** loss inhibiting agent. This activity is determined by means of an individual compound's pharmacokinetics and its minimal maximal effective dose in inhibition of **bone** loss using a protocol such as those referenced above.

SUMM In general an efective dosage for the activities of this invention, for example the treatment of **osteoporosis**, for the estrogen agonists/antagonists (when used in combination with a compound of Formula I of this invention) is in the. . .

IT Aging, animal

IT Obesity

IT **Osteoporosis**
(prepn. of nitrogen heterocyclic peptide analogs as growth-hormone secretagogues)

IT 193270-46-1P 193270-47-2P **193270-49-4P** 193270-50-7P
193270-51-8P 193270-52-9P 193270-53-0P 193270-54-1P 193270-55-2P
193270-56-3P 193270-57-4P 193270-58-5P 193270-59-6P 193270-60-9P
193270-61-0P 193270-62-1P 193270-63-2P 193270-64-3P 193270-68-7P
193270-70-1P 193270-71-2P 193270-72-3P 193270-73-4P 193270-76-7P
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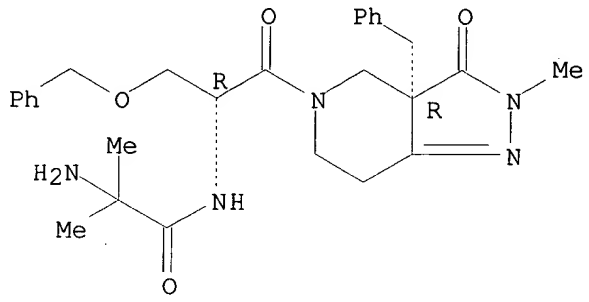
193273-84-6P 193273-85-7P 193273-86-8P 193273-87-9P 193273-88-0P
(prepn. of nitrogen heterocyclic peptide analogs as growth-hormone secretagogues)

IT **193270-49-4P 193273-65-3P 193273-66-4P**
193273-67-5P 193273-68-6P 193273-69-7P
(prepn. of nitrogen heterocyclic peptide analogs as growth-hormone secretagogues)

RN 193270-49-4 USPATFULL

CN Propanamide, 2-amino-N-[(1R)-2-[(3aR)-2,3,3a,4,6,7-hexahydro-2-methyl-3-oxo-3a-(phenylmethyl)-5H-pyrazolo[4,3-c]pyridin-5-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl-, monohydrochloride (9CI) (CA INDEX NAME)

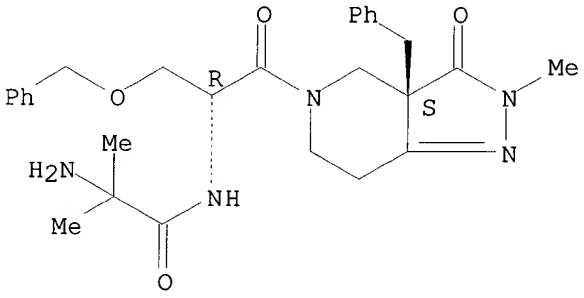
Absolute stereochemistry.



● HCl

RN 193273-65-3 USPATFULL
CN Propanamide, 2-amino-N-[(1R)-2-[(3aS)-2,3,3a,4,6,7-hexahydro-2-methyl-3-oxo-3a-(phenylmethyl)-5H-pyrazolo[4,3-c]pyridin-5-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl-, monohydrochloride (9CI) (CA INDEX NAME)

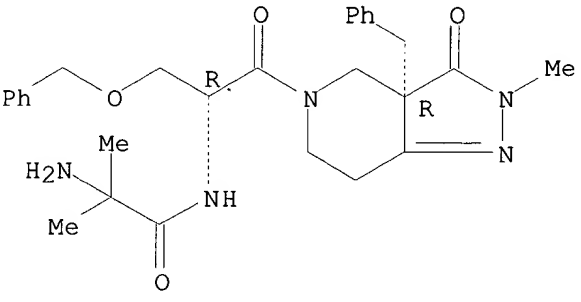
Absolute stereochemistry.



● HCl

RN 193273-66-4 USPATFULL
CN Propanamide, 2-amino-N-[(1R)-2-[(3aR)-2,3,3a,4,6,7-hexahydro-2-methyl-3-oxo-3a-(phenylmethyl)-5H-pyrazolo[4,3-c]pyridin-5-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

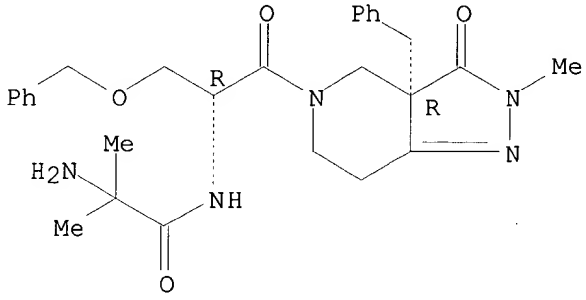


RN 193273-67-5 USPATFULL
CN Propanamide, 2-amino-N-[(1R)-2-[(3aR)-2,3,3a,4,6,7-hexahydro-2-methyl-3-oxo-3a-(phenylmethyl)-5H-pyrazolo[4,3-c]pyridin-5-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl-, monomethanesulfonate (9CI) (CA INDEX NAME)

CM 1

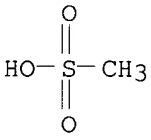
CRN 193273-66-4
CMF C28 H35 N5 O4

Absolute stereochemistry.



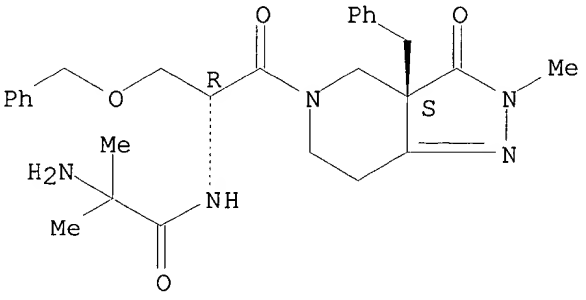
CM 2

CRN 75-75-2
CMF C H4 O3 S



RN 193273-68-6 USPATFULL
CN Propanamide, 2-amino-N-[(1R)-2-[(3aS)-2,3,3a,4,6,7-hexahydro-2-methyl-3-oxo-3a-(phenylmethyl)-5H-pyrazolo[4,3-c]pyridin-5-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



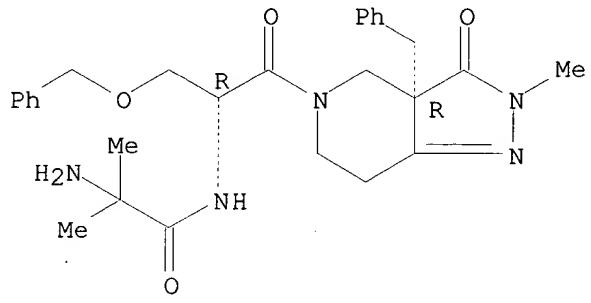
RN 193273-69-7 USPATFULL
CN Propanamide, 2-amino-N-[(1R)-2-[(3aR)-2,3,3a,4,6,7-hexahydro-2-methyl-3-oxo-3a-(phenylmethyl)-5H-pyrazolo[4,3-c]pyridin-5-yl]-2-oxo-1-

[(phenylmethoxy)methyl]ethyl]-2-methyl-, (2R,3R)-2,3-dihydroxybutanedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 193273-66-4
CMF C28 H35 N5 O4

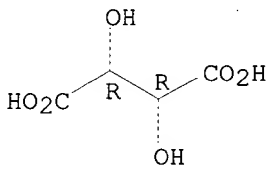
Absolute stereochemistry.



CM 2

CRN 87-69-4
CMF C4 H6 O6
CDES 1:R2:R*,R*

Absolute stereochemistry.



L73 ANSWER 4 OF 10 USPATFULL on STN
AN 2001:136801 USPATFULL
TI Growth-hormone secretagogues
IN Carpino, Philip A, Groton, CT, United States
DaSilva-Jardine, Paul A, Providence, RI, United States
Lefker, Bruce A, Gales Ferry, CT, United States
Ragan, John A, Gales Ferry, CT, United States
PA **Pfizer Inc.**, New York, NY, United States (U.S. corporation)
PI US 6278000 B1 20010821
AI US 1999-470668 19991222 (9)
RLI Division of Ser. No. US 1999-259776, filed on 1 Mar 1999, now patented, Pat. No. US 6124264 Division of Ser. No. US 68566
PRAI US 1995-9469P 19951228 (60) <--
DT Utility
FS GRANTED
EXNAM Primary Examiner: McKane, Joseph K.; Assistant Examiner: Wright, Sonya
LREP Richardson, Peter C., Benson, Gregg C., Ronau, Robert T.
CLMN Number of Claims: 5
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 4128
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention is directed to compounds of the formula ##STR1##

and the pharmaceutically-acceptable salts thereof, where the substituents are as defined in the Specification, which are growth hormone secretogogues and which increase the level of endogenous growth hormone. The compounds of this invention are useful for the treatment and prevention of **osteoporosis**, congestive heart failure, frailty associated with aging, obesity; accelerating **bone fracture** repair, attenuating protein catabolic response after a major operation, reducing cachexia and protein loss due to chronic illness, accelerating wound healing, or accelerating the recovery of burn patients or patients having undergone major surgery; improving muscle strength, mobility, maintanence of skin thickness, metabolic homeostasis or renal homeostasis. The compounds of the present invention are also useful in treating **osteoporosis** when used in combination with: a bisphosphonate compound such as alendronate; estrogen, premarin, and optionally progesterone, an estrogen agonist or antagonist; or calcitonin, and pharmaceutical compositions useful therefor. Further, the present invention is directed to pharmaceutical composition useful for increasing the endogenous production or release of growth hormone in a human or other animal which comprises an effective amount of a compound of the present invention and a growth hormone secretagogue selected from GHRP-6, Hexarelin, GHRP-1, growth hormone releasing factor (GRF), IGF-1, IGF-2 or B-HT920. The invention is also directed to intermediates useful in the preparation of compounds of formula I.

PA **Pfizer Inc.**, New York, NY, United States (U.S. corporation)

PRAI US 1995-9469P 19951228 (60) <--

AB . . . increase the level of endogenous growth hormone. The compounds of this invention are useful for the treatment and prevention of **osteoporosis**, congestive heart failure, frailty associated with aging, obesity; accelerating **bone fracture** repair, attenuating protein catabolic response after a major operation, reducing cachexia and protein loss due to chronic illness, accelerating wound. . . maintanence of skin thickness, metabolic homeostasis or renal homeostasis. The compounds of the present invention are also useful in treating **osteoporosis** when used in combination with: a bisphosphonate compound such as alendronate; estrogen, premarin, and optionally progesterone, an estrogen agonist or. . .

SUMM This invention relates to dipeptide compounds which are growth hormone secretagogues and are useful for the treatment and prevention of **osteoporosis**.

SUMM . . . the truncal region. Decreased skeletal and cardiac muscle mass and muscle strength lead to a significant reduction in exercise capacity. **Bone** density is also reduced. Administration of exogenous growth hormone has been shown to reverse many of the metabolic changes. Additional. . .

SUMM The compounds of WO 94/11012 and WO 94/13696 are reported to be useful in the treatment of **osteoporosis** in combination with parathyroid hormone or a bisphosphonate.

SUMM a method for the treatment or prevention of **osteoporosis** which comprises administering to a human or other animal in need of such treatment or prevention an amount of a compound of Formula I which is effective in treating or preventing **osteoporosis**;

SUMM a method for the treatment or prevention of **osteoporosis** which comprises administering to a human or other animal with **osteoporosis** a combination of a bisphosphonate compound such as alendronate, and especially preferred is the bisphosphonate compound ibandronate, and a compound. . .

SUMM a method for the treatment or prevention of **osteoporosis** which comprises administering to a human or other animal with **osteoporosis** a combination of estrogen or Premarin.RTM. and a compound of Formula I and optionally progesterone;

SUMM a method for the treatment of **osteoporosis** which comprises administering to a human or other animal with **osteoporosis** a combination of an estrogen against or antagonist such as tamoxifen, droloxifene, raloxifene and idoxifene and a compound of Formula. . .

SUMM a particularly preferred method for the treatment of **osteoporosis** comprises administering to a human or other animal with **osteoporosis** a combination of an estrogen agonist or antagonist such as Cis-6-(4-fluoro-phenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol;

SUMM a method for the treatment of **osteoporosis** which comprises administering to a human or other animal with **osteoporosis** a combination of calcitonin and a compound of Formula I;

SUMM In another aspect, this invention provides methods for accelerating **bone fracture** repair, attenuating protein catabolic response after a major operation, reducing cachexia and protein loss due to chronic illness such as. . . effective in promoting release of endogenous growth hormone; of the instant method a preferred method of use is to accelerate **bone fracture** repair or for accelerating the recovery of patients having undergone major surgery.

SUMM . . . efficiency of animals raised for meat production to improve carcass quality; to increase milk production in dairy cattle; improvement of **bone** or wound healing and improvement in vital organ function. The compounds of the present invention by inducing endogenous GH secretion. . .

SUMM . . . Formula I or another compound which exhibits a different activity, e.g., an antibiotic growth, permittant or an agent to treat **osteoporosis** or with other pharmaceutically active materials wherein the combination enhances efficacy and minimizes side effects.

SUMM . . . follows: stimulating growth hormone release in elderly humans; treating growth hormone deficient adults; preventing catabolic side effects of glucocorticoids, treating **osteoporosis**, stimulating the immune system, acceleration of wound healing, accelerating **bone fracture** repair, treating growth retardation, treating congestive heart failure as disclosed in PCT publications WO 95/28173 and WO 95/28174 (an example. . . as gastrointestinal surgery; treating intrauterine growth retardation, skeletal dysplasia, hypercortisonism and Cushings syndrome; replacing growth hormone in stressed patients; treating **osteochondrodysplasias**, Noonans syndrome, sleep disorders, Alzheimer's disease, delayed wound healing, and psychosocial deprivation; treating of pulmonary dysfunction and ventilator dependency; attentuating. . . improving muscle strength, increasing muscle mass, mobility, maintenance of skin thickness, metabolic homeostasis, renal hemeostasis in the frail elderly; stimulating **osteoblasts**, **bone** remodelling, and cartilage growth; treating neurological diseases such as peripheral and drug induced neuropathy, Guillian-Barre Syndrome, amyotrophic lateral sclerosis, multiple. . .

SUMM . . . one times the dose levels which are effective when these compounds and secretagogues are used singly. Combined therapy to inhibit **bone** resorption, prevent **osteoporosis**, reduce skeletal **fracture**, enhance the healing of **bone fractures**, stimulate **bone** formation and increase **bone** mineral density can be effectuated by combinations of bisphosphonates and the growth hormone secretagogues of this invention, see PCT publication. . . The use of bisphosphonates for these utilities has been reviewed, for example, by Hamdy, N.A.T., Role of Bisphosphonates in Metabolic **Bone** Diseases, Trends in Endocrinol. Metab., 1993, 4, pages 19-25. Bisphosphonates with these utilities include but are not limited to alendronate,. . . invention of between 0.01 mg/kg to 20 mg/kg of body weight are administered to patients to obtain effective treatment of **osteoporosis**.

SUMM . . . the second compound of this invention. The term estrogen agonist/antagonist refers to compounds which bind with the estrogen

receptor, inhibit **bone** turnover and prevent **bone** loss. In particular, estrogen agonists are herein defined as chemical compounds capable of binding to the estrogen receptor sites in. . . activities are readily determined by those skilled in the art according to standard assays including estrogen receptor binding assays, standard **bone** histomorphometric and densitometer methods (see Eriksen E. F. et al., **Bone** Histomorphometry, Raven Press, New York, 1994, pages 1-74; Grier S. J. et al., The Use of Dual-Energy X-Ray Absorptiometry In Animals, Inv. Radiol., 1996, 31(1):50-62; Wahner H. W. and Fogelman I., The Evaluation of **Osteoporosis**: Dual Energy X-Ray Absorptiometry in Clinical Practice., Martin Dunitz Ltd., London 1994, pages 1-296). A variety of these compounds are. . .

SUMM The amount of the anti-resorptive agent to be used is determined by its activity as a **bone** loss inhibiting agent. This activity is determined by means of an individual compound's pharmacokinetics and its minimal maximal effective dose in inhibition of **bone** loss using a protocol such as those reference above.

SUMM In general an effective dosage for the activities of this invention, for example the treatment of **osteoporosis**, for the estrogen agonists/antagonists (when used in combination with a compound of Formula I of this invention) is in the. . .

IT Aging, animal

IT Obesity

IT **Osteoporosis**
(prepn. of nitrogen heterocyclic peptide analogs as growth-hormone secretagogues)

IT 193270-46-1P 193270-47-2P **193270-49-4P** 193270-50-7P
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193270-78-9P 193270-81-4P 193270-86-9P 193270-90-5P 193270-94-9P
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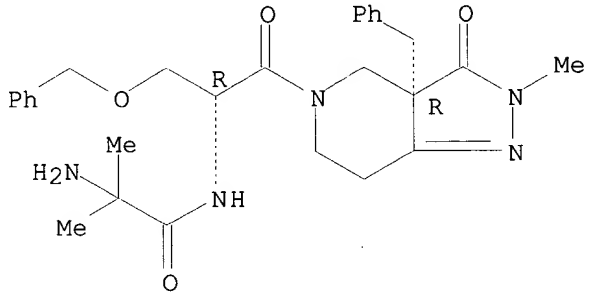
193273-79-9P 193273-80-2P 193273-81-3P 193273-82-4P 193273-83-5P
193273-84-6P 193273-85-7P 193273-86-8P 193273-87-9P 193273-88-0P
(prepn. of nitrogen heterocyclic peptide analogs as growth-hormone secretagogues)

IT **193270-49-4P 193273-65-3P 193273-66-4P**
193273-67-5P 193273-68-6P 193273-69-7P
(prepn. of nitrogen heterocyclic peptide analogs as growth-hormone secretagogues)

RN 193270-49-4 USPATFULL

CN Propanamide, 2-amino-N-[(1R)-2-[(3aR)-2,3,3a,4,6,7-hexahydro-2-methyl-3-oxo-3a-(phenylmethyl)-5H-pyrazolo[4,3-c]pyridin-5-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

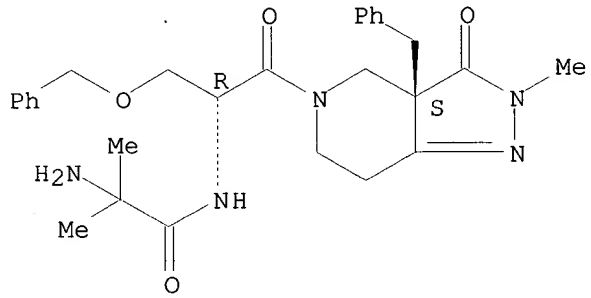


● HCl

RN 193273-65-3 USPATFULL

CN Propanamide, 2-amino-N-[(1R)-2-[(3aS)-2,3,3a,4,6,7-hexahydro-2-methyl-3-oxo-3a-(phenylmethyl)-5H-pyrazolo[4,3-c]pyridin-5-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

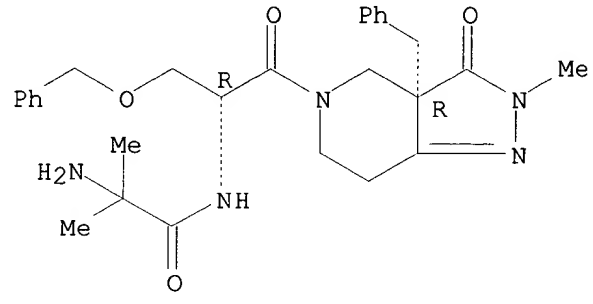


● HCl

RN 193273-66-4 USPATFULL

CN Propanamide, 2-amino-N-[(1R)-2-[(3aR)-2,3,3a,4,6,7-hexahydro-2-methyl-3-oxo-3a-(phenylmethyl)-5H-pyrazolo[4,3-c]pyridin-5-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

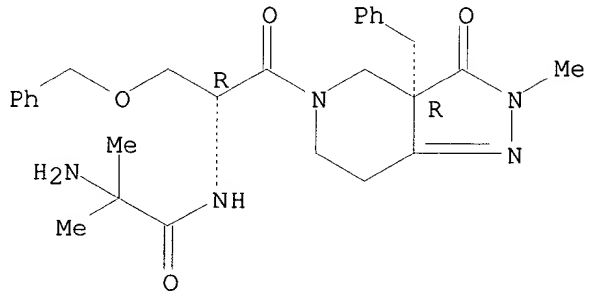


RN 193273-67-5 USPATFULL
CN Propanamide, 2-amino-N-[(1R)-2-[(3aR)-2,3,3a,4,6,7-hexahydro-2-methyl-3-oxo-3a-(phenylmethyl)-5H-pyrazolo[4,3-c]pyridin-5-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl-, monomethanesulfonate (9CI) (CA INDEX NAME)

CM 1

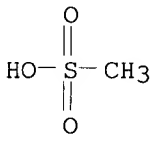
CRN 193273-66-4
CMF C28 H35 N5 O4

Absolute stereochemistry.



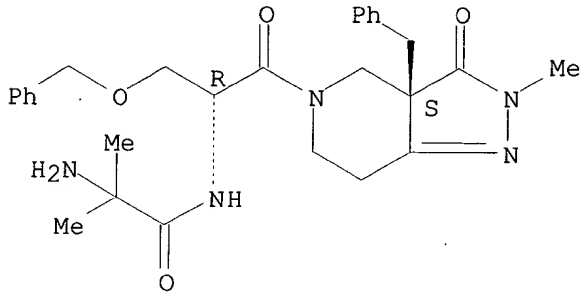
CM 2

CRN 75-75-2
CMF C H4 O3 S



RN 193273-68-6 USPATFULL
CN Propanamide, 2-amino-N-[(1R)-2-[(3aS)-2,3,3a,4,6,7-hexahydro-2-methyl-3-oxo-3a-(phenylmethyl)-5H-pyrazolo[4,3-c]pyridin-5-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

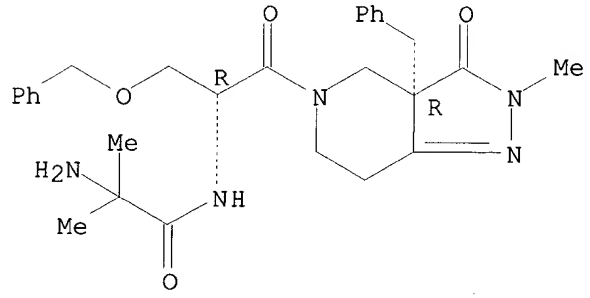


RN 193273-69-7 USPATFULL
CN Propanamide, 2-amino-N-[(1R)-2-[(3aR)-2,3,3a,4,6,7-hexahydro-2-methyl-3-oxo-3a-(phenylmethyl)-5H-pyrazolo[4,3-c]pyridin-5-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl-, (2R,3R)-2,3-dihydroxybutanedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 193273-66-4
CMF C28 H35 N5 O4

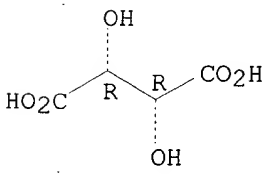
Absolute stereochemistry.



CM 2

CRN 87-69-4
CMF C4 H6 O6
CDES 1:R2:R*,R*

Absolute stereochemistry.



L73 ANSWER 5 OF 10 USPATFULL on STN
AN 2001:119297 USPATFULL
TI Combination therapy for **osteoporosis**
IN **Ke, Hua Zhu**, Ledyard, CT, United States
Thompson, David D., Gales Ferry, CT, United States
PI US 2001009920 A1 20010726

AI US 2000-736051 A1 20001213 (9)
RLI Division of Ser. No. US 1998-117972, filed on 11 Aug 1998, PENDING A 371 of International Ser. No. WO 1996-IB1462, filed on 23 Dec 1996, UNKNOWN
PRAI US 1996-12412P 19960228 (60) <--
DT Utility
FS APPLICATION
LREP Gregg C. Benson, Pfizer Inc., Patent Department, MS 4159, Eastern Point Road, Groton, CT, 06340
CLMN Number of Claims: 92
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 2509
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Pharmaceutical combination compositions including certain estrogen agonists/antagonists and prostaglandins or prostaglandin agonists/antagonists. The compositions are useful for the treatment of **bone** disorders including **osteoporosis**.
TI Combination therapy for **osteoporosis**
IN **Ke, Hua Zhu**, Ledyard, CT, United States
IN **Thompson, David D.**, Gales Ferry, CT, United States
PRAI US 1996-12412P 19960228 (60) <--
AB Pharmaceutical combination compositions including certain estrogen agonists/antagonists and prostaglandins or prostaglandin agonists/antagonists. The compositions are useful for the treatment of **bone** disorders including **osteoporosis**.
SUMM [0001] This invention relates to a pharmaceutical combination of estrogen agonists/antagonists and agents that stimulate **bone** formation and increase **bone** mass, kits containing such combinations and the use of such combinations to treat conditions which present with low **bone** mass in mammals, including humans.
SUMM [0002] **Osteoporosis** is a systemic skeletal disease, characterized by low **bone** mass and deterioration of **bone** tissue, with a consequent increase in **bone** fragility and susceptibility to **fracture**. In the U.S., the condition affects more than 25 million people and causes more than 1.3 million **fractures** each year, including 500,000 spine, 250,000 hip and 240,000 wrist **fractures** annually. Hip **fractures** are the most serious, with 5-20% of patients dying within one year, and over 50% of survivors being incapacitated.
SUMM [0003] The elderly are at greatest risk of **osteoporosis**, and the problem is therefore predicted to increase significantly with the aging of the population. Worldwide **fracture** incidence is forecast to increase threefold over the next 60 years, and one study estimates that there will be 4.5 million hip **fractures** worldwide in 2050.
SUMM [0004] Women are at greater risk of **osteoporosis** than men. Women experience a sharp acceleration of **bone** loss immediately following menopause. Other factors that increase **bone** loss leading to **osteoporosis** include smoking, alcohol abuse, a sedentary lifestyle and low calcium intake.
SUMM [0005] Estrogen is the agent of choice in preventing **osteoporosis** or post menopausal **bone** loss in women. In addition, Black, et al. in EP 06051931A1 report that estrogen, particularly when taken orally, lowers plasma. . . effects of estrogen. The significant undesirable side effects associated with estrogen therapy support the need to develop alternative therapies for **osteoporosis** that have the desirable beneficial effect on serum LDL but do not cause undesirable side effects.
SUMM [0006] Recently, a number of estrogen agonists/antagonists have been proposed for treatment of **osteoporosis**. It has been reported (**Osteoporosis** Conference Scrip No. 1812/13 Apr. 16/20, 1993, p. 29) that raloxifene, 6hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, mimics the favorable

action of estrogen on **bone** and lipids but, unlike estrogen, has minimal uterine stimulatory effect. [Black, L. J. et al., Raloxifene (LY139481 Hcl) Prevents **Bone** Loss and Reduces Serum Cholesterol Without Causing Uterine Hypertrophy in Ovariectomized Rats, J. Clin. Invest., 1994, 93:6369].

SUMM [0007] Also, tamoxifen, 1-(4-.beta.-dimethylaminoethoxyphenyl)-1,2-diphenyl-but-1-ene, is an antiestrogen that is proposed as an **osteoporosis** agent which has a palliative effect on breast cancer, but is reported to have some estrogenic activity in the uterus.. . .

SUMM . . . No. 5,254,594 (the disclosure of which is hereby incorporated by reference) discloses the use of droloxifene for the treatment of **bone** diseases including **osteoporosis**.

SUMM [0009] Agents such as droloxifene prevent **bone** loss and thereby reduce the risk of **fracture** without estrogen's side effects. However, estrogen and estrogen agonists alone are only expected to reduce the **fracture** risk by about 50% leaving approximately 50% of ostepenic women still at risk for an **osteoporotic fracture**.

SUMM [0010] Nonestogen agonists/antagonists such as bisphosphonates are also proposed for the treatment of **osteoporosis**. For example, Fosanax.RTM. is a bisphosphonate that is currently marketed for the treatment of **osteoporosis**. Other bisphosphonates currently undergoing regulatory review include risedronate, tiludronate, and ibandronate.

SUMM [0011] Frost et al. in "Treatment of **Osteoporosis** by Manipulation of Coherent **Bone** Cell Populations", Clinical Orthopedics and Related Research, 143, 227 (1979) discloses a theoretical model that suggests it should be possible to synchronize the activity and metabolism of **bone** cells by administering a **bone** cell activating agent first, followed by a bons resorption inhibiting agent and then normal **bone** formation is allowed to occur.

SUMM [0012] Tang et al., Restoring and Maintaining **Bone** in **Osteogenic** Female Rat Skeleton: I. Changes in **Bone** Mass and Structure, J. **Bone** Mineral Research 7 (9), p1093-1104, 1992 discloses data for the lose, restore and maintain (LRM) concept, a practical approach for reversing existing **osteoporosis**. The LRM concept uses anabolic agents to restore **bone** mass and architecture (+phase) and then switches to an agent with the established ability to maintain **bone** mass, to keep the new **bone** (+/-phase). The rat study utilized PGE.sub.2 and risedronate, a bisphosphonate, to show that most of the new cancellous and cortical **bone** induced by PGE.sub.2 can be maintained for at least 60 days after discontinuing PGE.sub.2 by administering risedronate.

SUMM [0013] Combinations of bisphosphonates and prostaglandins for the treatment of **osteoporosis** are disclosed. E.P. App. No. 0 381 296 teaches the use of a kit wherein a **bone** activating period or treatment regime is followed by a **bone** resorption inhibiting regime. Examples of **bone** activating compounds cited in this reference include parathyroid hormone (PTH), inorganic phosphate, growth hormone, fluoride, thyroid hormone (e.g., thyroxin), certain. . . vitamin D metabolites and prostaglandins (PGE.sub.2 in a dose regime of 10 mg/kg per day). Polyphosphonates are disclosed as the **bone** resorption inhibiting agents.

SUMM [0014] PCT/US93/08529 discloses the simultaneous delivery of a **bone** activating agent such as a prostaglandin that is chemically coupled to a **bone** resorption inhibiting compound which selectively delivers the **bone** activating agent to the target area. Upon gradual hydrolysis of the novel compound, the hydrolyzed products are able to provide **bone** resorption inhibiting activity (via the bisphosphonates) and **bone** growth or

stimulating activity (via PGE.sub.2).

SUMM . . . E2 and risedronate (a bisphosphonate) was studied in Lin et al., Effects of Prostaglandin E2 and Risedronate Administration on Cancellous **Bone** in Older Female Rats, **Bone** 15 (5), p489-496, 1994.

SUMM . . . Monogr. Nat. Cancer Inst. (16), 161-167, 1994, states "The use of several nonestrogen approaches for the prevention and treatment of **osteoporosis** has been promising. Traditional recommendations to maintain skeletal integrity, such as weight-bearing exercise; a diet rich in calcium and limited. . .

SUMM [0018] Thus, although there exist a variety of **osteoporosis** therapies there is a continuing need and a continuing search in this field of art for alternative therapies due to only limited success of current therapies in reducing **osteoporotie fractures**

.

SUMM . . . agonists/antagonists and anabolic agents and for the use of such compositions for the treatment of conditions which present with low **bone** mass, including **osteoporosis** in mammals (e.g., humans, particularly women).

SUMM [0030] Another aspect of this invention is a method for treating mammals which present with low **bone** mass comprising administering to a mammal having a condition which presents with low **bone** mass

SUMM [0042] A preferred aspect of this method is wherein the condition which presents with low **bone** mass is **osteoporosis.**

SUMM . . . compound alone and the amount of the second compound alone is insufficient to achieve the therapeutic effects of increase in **bone** formation and decrease in **bone** resorption if administered simultaneously and wherein the combined effect of the amounts of the first and second compounds is greater. . .

SUMM [0051] Yet another aspect of this invention is a synergistic method for treating mammals which present with low **bone** mass comprising administering to a mammal having a condition which presents with low **bone** mass

SUMM . . . compound alone and the amount of the second compound alone is insufficient to achieve the therapeutic effects of increase in **bone** formation and decrease in **bone** resorption if administered simultaneously and wherein the combined effect of the amounts of the first and second compounds is greater. . .

SUMM [0055] Another aspect of this invention is a kit containing a treatment for a condition which presents with low **bone** mass comprising:

SUMM [0061] b. a therapeutically effective amount of a second compound, said second compound being sodium fluoride or N-[1-(R)-[1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide:**MK-677.**

SUMM [0063] Another aspect of this invention is directed to a method for treating mammals which present with low **bone** mass comprising administering to a mammal having a condition which presents with low **bone** mass

SUMM [0065] b. a therapeutically effective amount of a second compound, said second compound being sodium fluoride or N-[1-(R)-[1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide:**MK-677.**

SUMM [0067] Another preferred aspect of this method is wherein the condition which presents with low **bone** mass is **osteoporosis.**

SUMM [0074] b. an amount of a second compound, said second compound being sodium fluoride or N-[1(R)-[1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide:**MK-677**

SUMM . . . compound alone and the amount of the second compound alone is insufficient to achieve the therapeutic effects of increase in **bone** formation and decrease in **bone** resorption if

administered simultaneously and wherein the combined effect of the amounts of the first and second compounds is greater. . .

SUMM [0077] Yet another aspect of this invention is a synergistic method for treating mammals which present with low **bone** mass comprising administering to a mammal having a condition which presents with low **bone** mass

SUMM [0079] b. an amount of a second compound, said second compound being sodium fluoride or N-[1(R)-[1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide:**MK-677**

SUMM . . . compound alone and the amount of the second compound alone is insufficient to achieve the therapeutic effects of increase in **bone** formation and decrease in **bone** resorption if administered simultaneously and wherein the combined effect of the amounts of the first and second compounds is greater. . .

SUMM [0082] Another aspect of this invention is a kit containing a treatment for a condition which presents with low **bone** mass comprising:

SUMM [0084] b. a therapeutically effective amount of sodium fluoride or N-[1-(R)-[1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2amino-2-methylpropanamide: **MK-677** and a pharmaceutically acceptable carrier in a second unit dosage form; and

SUMM [0097] Yet another aspect of this invention is a method for treating mammals which present with low **bone** mass comprising administering to a mammal having a condition which presents with low **bone** mass

SUMM [0107] A preferred aspect of this method is wherein the condition which presents with low **bone** mass is **osteoporosis**.

SUMM . . . compound alone and the amount of the second compound alone is insufficient to achieve the therapeutic effects of increase in **bone** formation and decrease in **bone** resorption if administered simultaneously and wherein the combined effect of the amounts of the first and second compounds is greater. . .

SUMM [0123] Yet another aspect of this invention is a synergistic method for treating mammals which present with low **bone** mass comprising administering to a mammal having a condition which presents with low **bone** mass

SUMM . . . compound alone and the amount of the second compound alone is insufficient to achieve the therapeutic effects of increase in **bone** formation and decrease in **bone** resorption if administered simultaneously and wherein the combined effect of the amounts of the first and second compounds is greater. . .

SUMM [0134] Yet another aspect of this invention is a kit containing a treatment for a condition which presents with low **bone** mass comprising:

SUMM . . . art will recognize that other anti-resorptive agents (bisphosphonate, estrogen, estradiol, premarin, eston, estriol or 17.alpha.- or 17.beta.-ethynyl estradiol) and other **bone** anabolic agents (androgen, androgen agonist/antagonist) may be used together or with any of the agents described herein in this invention. . .

SUMM [0151] For example, the anti-resorptive agent droloxifene may be combined with an individual **bone** anabolic agent such as parathyroid hormone, growth hormone or growth hormone secretagogues.

SUMM [0152] The phrase "condition which presents with low **bone** mass" refers to a condition where the level of **bone** mass is below the age specific normal as defined in standards by the World Health Organization "Assessment of **Fracture** Risk and its Application to Screening for Postmenopausal **Osteoporosis** (1994), Report of a World Health Organization Study Group. World Health Organization Technical Series-843". Childhood idiopathic and primary **osteoporosis** are also included. Included in the treatment of **osteoporosis** is the prevention or attenuation of long term

complications such as curvature of the spine, loss of height, prosthetic surgery, and prevention of prostate malfunctioning. Also included is increasing the **bone fracture** healing rate and enhancing the rate of successful **bone** grafts. Also included is periodontal disease and alveolar **bone** loss.

SUMM [0153] The phrase "condition which presents with low **bone** mass" also refers to a mammal known to have a significantly higher than average chance of developing such diseases as are described above including **osteoporosis** (e.g., post-menopausal women, men over the age of 60, and persons being treated with drugs known to cause **osteoporosis** as a side effect (such as glucocorticoid)).

SUMM [0154] Those skilled in the art will recognize that the term **bone** mass actually refers to one mass per unit area which is sometimes (although not strictly correctly) referred to as **bone** mineral density.

SUMM [0165] The pharmaceutical compositions of this invention result in a more rapid and higher magnitude **bone** mass gain than is achievable with the same doses of estrogen agonists/antagonists as described above alone or an agent which stimulates an increase in **bone** mineral density as described above alone. Thus, these combinations have a synergistic action, increasing **bone** mass and decreasing **fracture** rates to a greater extent than is achievable through use of either agent alone. This invention makes a significant contribution to the art by providing compositions and methods that increase and maintain **bone** mass resulting in prevention, retardation, and/or regression of **osteoporosis** and related **bone** disorders.

DETD . . . the first compound of this invention. The term estrogen agonist/antagonist refers to compounds which bind with the estrogen receptor, inhibit **bone** turnover and prevent **bone** loss. Such activities are readily determined by those skilled in the art according to standard assays including estrogen receptor binding assays (see in Vitro Estrogen Receptor Binding Assay hereinafter), standard **bone** histomorphometric and densitometer methods (see Estrogen Agonist/Antagonist Protocol hereinafter, and Eriksen E. F. et al., **Bone** Histomorphometry, Raven Press, New York, 1994, pages 1-74; Grier S. J. et. al., The Use of Dual-Energy X-Ray Absorptiometry In Animals, Inv. Radiol., 1996,31(1):50-62; Wahner H. W. and Fogelman I., The Evaluation of **Osteoporosis**: Dual Energy X-Ray Absorptiometry in Clinical Practice., Martin Dunitz Ltd., London 1994, pages 1-296). A variety of these compounds are. . .

DETD [0286] The second compound of this invention may be any compound as described below that augments **bone** mass to a level which is above the **bone fracture** threshold (as detailed in the World Health Organization Study World Health Organization, "Assessment of **Fracture** Risk and its Application to Screening for Postmenopausal **Osteoporosis** (1994). Report of a WHO Study Group. World Health Organization Technical Series 843").

DETD . . . which are analogs of the natural prostaglandins PGD.sub.1, PGD.sub.2, PGE.sub.2, PGE.sub.1 and PGF.sub.2.alpha. which are useful in the treatment of **osteoporosis**. These compounds bind to the prostaglandin receptors. Such binding is readily determined by those skilled in the art according to. . .

DETD [0291] Norrdin et al., The Role of Prostaglandins in **Bone** In Vivo, Prostaglandins Leukotriene Essential Fatty Acids 41, 139-150, 1990 is a review of **bone** active prostaglandins.

DETD . . . for Prostaglandin E.sub.2, Biochemical and Biophysical Research Communications, 1993, 197(1):263-270) and mimic the action of prostaglandin in vivo (e.g., stimulate **bone** formation and increase **bone** mass). Such actions are readily determined by those skilled in the art according to standard assays (e.g., see Anabolic Agent Protocol described hereinafter and Erksen E. F. et al., **Bone** Histomorphometry, Raven Press, New York, 1994, pages 1-74;

Grier S. J. et. al., The Use of Dual-Energy X-Ray Absorptiometry In Animals, Inv. Radiol., 1996, 31(1):50-62; Wahner H. W. and Fogelman I., The Evaluation of **Osteoporosis**: Dual Energy X-Ray Absorptiometry In Clinical Practice., Martin Dunitz Ltd., London 1994, pages 1-296). A variety of these compounds are. . .

DETD [0293] Commonly assigned U.S. Pat. No. 3,932,389 (the disdosure of which is hereby incorporated by reference) discloses 2-descarboxy-2-(tetrazol-5-yl)-11-desoxy-15-substituted-omega-pentanorprostaglandins useful for **bone** formation activity.

DETD . . . assigned U.S. Pat. No. 4,018,892 (the disclosure of which is hereby incorporated by reference) discloses 16-aryl-13,14-dihydro-PGE.sub.2 p-biphenyl esters useful for **bone** formation activity.

DETD [0295] Commonly assigned U.S. Pat. No. 4,219,483 (the disclosure of which is hereby incorporated by reference) discloses-2,3,6-substituted-4-pyrones useful for **bone** formation activity.

DETD [0296] Commonly assigned U.S. Pat. No. 4,132,847 (the disclosure of which is hereby incorporated by reference) discloses 2,3,6-substituted-4-pyrones useful for **bone** formation activity.

DETD [0297] U.S. Pat. No. 4,000,309 (the disclosure of which is hereby incorporated by reference) discloses 16-aryl-13,14-dihydro-PGE.sub.2 p-biphenyl esters useful for **bone** formation activity.

DETD [0298] U.S. Pat. No. 3,982,016 (the disclosure of which is hereby incorporated by reference) discloses 16-aryl-13,14-dihydro-PGE.sub.2 p-biphenyl esters useful for **bone** formation activity.

DETD [0299] U.S. Pat. No. 4,621,100 (the disclosure of which is hereby incorporated by reference) discloses substituted cyclopentanes useful for **bone** formation activity.

DETD [0300] U.S. Pat. No. 5,216,183 (the disclosure of which is hereby incorporated by reference) discloses cyclopentanones useful for **bone** formation activity.

DETD . . . in the art according to biological protocols (e.g., see Anabolic Agent Protocol described hereinafter and Eriksen E. F. et al., **Bone** Histomorphometry, Raven Press, New York, 1994, pages 1-74; Grier S. J. et. al., The Use of Dual-Energy X-Ray Absorptiometry in Animals, Inv. Radiol., 1996, 31(1):50-62; Wahner H. W. and Fogelman I., The Evaluation of **Osteoporosis**: Dual Energy X-Ray Absorptiometry in Clinical Practice., Martin Dunitz Lid., London 1994, pages 1-296).

DETD . . . invention. The term parathyroid hormone refers to parathyrold hormone, fragments or metabolites thereof and structural analogs thereof which can stimulate **bone** formation and increase **bone** mass. Such functional activity is readily determined by those skilled in the art according to standard assays (e.g., see Anabolic Agent Protocol described hereinafter and Eriksen E. F. et al., **Bone** Histomorphometry, Raven Press, New York, 1994, pages 1-74; Grier S. J. et. al., The Use of Dual-Energy X-Ray Absorptiometry In Animals, Inv. Radiol., 1996,31(1):50-62; Wahner H. W. and Fogelman I., The Evaluation of **Osteoporosis**: Dual Energy X-Ray Absorptiometry in Clinical Practice., Martin Dunitz Ltd., London 1994, pages 1-296). A variety of these compounds are. . .

DETD [0303] "Human Parathyroid Peptide Treatment of Vertebral **Osteoporosis**", **Osteoporosis** Int., 3, (Supp 1):199-203.

DETD [0304] "PTH 1-34 Treatment of **Osteoporosis** with Added Hormone Replacement Therapy: Biochemical, Kinetic and Histological Responses" **Osteoporosis** Int. 1:162-170.

DETD . . . secretagogue refers to compounds which stimulate the release of growth hormone or mimic the action of growth hormone (e.g., increase **bone** formation leading to increased **bone** mass). Such actions are readily determined by those skilled in the art according to standard assays (e.g., as described hereinafter).. . .

DETD [0306] In particular a preferred growth hormone secretagogue is

N-[1-(R)-[1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidln]-1'-yl)cabonyl]-2-(phenytmethyloxy)ethyl]-2-amino-2-methylpropanamide: **MK-677**.

DETD [0317] The pharmaceutical combinations and methods of this invention are all adapted to therapeutic use as agents that either activate **bone** turnover or prevent **bone** resorption or increase **bone** formation in mammals, particularly humans. Since these functions are closely related to the development of **osteoporosis** and **bone** related disorders, these combinations, by virtue of their action on **bone**, prevent, arrest, regress or reverse **osteoporosis**.

DETD . . . utility of the compounds of the present invention as medical agents in the treatment of conditions which present with low **bone** mass (e.g., **osteoporosis**) in mammals (e.g. humans, particularly the female) is demonstrated by the activity of the compounds of this invention in conventional. . .

DETD . . . months). In the castrated rats, treatment can be started at the next day after surgery (for the purpose of preventing **bone** loss) or at the time **bone** loss has already occurred (for the purpose of restoring **bone** mass).

DETD [0320] The following protocols are described as using PGE2 as the **bone** anabolic agent and droloxifene as the antiresorptive agent, however, other anabolic agents and antiresorptive agents may be tested in the. . .

DETD . . . sham-operated or ovariectomized (OVX) at month 0. Three months post-surgery, OVX rats receive either Prostaglandin E.sub.2 (PGE.sub.2), a known anabolic **bone** agent, at 3 mg/kg/day (subcutaneously injection), or PGE.sub.2 at 3 mg/kg/day (subcutaneously injection) combined with droloxifene (DRO) at 10 mg/kg/day. . .

DETD . . . Droloxifene solution is given daily p.o. at 1 ml/rat. All rats are given subcutaneous injections of 10 mg/kg kalcein (fluorochrome **bone** marker, Sigma Chemical Co. St. Louis Mo.) twelve and two days before death to examine the dynamic changes in **bone** tissues.

DETD [0336] Femoral **Bone** Mineral Measurements

DETD . . . is 5.08.times.1.902 cm, resolution is 0.0254.times.0.0127 cm and scan speed is 7.25 mm/second. The femoral scan images are analyzed and **bone** area, **bone** mineral content (BMC), and **bone** mineral density (BMD) of whole femora (WF), distal femoral metaphyses (DFM), femoral shaft (FS), and proximal femora (PF) are determined.

DETD [0338] LumbarVertebral **Bone** Mineral Measurements

DETD . . . Inc., Waltham, Mass.) equipped with a "Regional High Resolution Scan" software (Hologic, Inc., Waltham, Mass.) is used to determined the **bone** area, **bone** mineral content (BMC), and **bone** mineral density (BMD) of whole lumbar spine and each of the six lumbar vertebrae (LV1-6) in the anesthetized rats. The. . . resolution is 0.0254.times.0.0127 cm, and scan speed is 7.25 mm/sec. The whole lumbar spine scan image is obtained and analyzed. **Bone** area (BA), and **bone** mineral content (BMC) is determined, and **bone** mineral density is calculated (MBC divided by BA) for the whole lumbar spine and each of the six lumbar vertebrae. . .

DETD [0340] Proximal Tibial Metaphyseal Cancellous **Bone** Histomorphometric Analyses

DETD . . . using Reichert-Jung Polycut S microtome. One 4 .mu.m and one 10 .mu.m sections from each rat is used for cancellous **bone** histomorphometry. The 4 .mu.m sections is stained with modified Masson's Trichrome stain while the 10 .mu.m sections remained unstained.

DETD . . . in order to restrict measurements to the secondary spongiosa. The 4 .mu.m sections are used to determine indices related to **bone** volume, **bone** structure, and **bone** resorption, while the 10 .mu.m sections are used to determine indices related to **bone** formation and **bone** turnover.

DETD [0343] I. Measurements and calculations related to trabecular **bone** volume and structure

DETD [0346] 2. Trabecular **bone** area (BV, mm.sup.2): total area of trabeculae within TV.

DETD [0347] 3. Trabecular **bone** perimeter (BS, mm): the length of total perimeter of trabeculae.

DETD [0348] 4. Trabecular **bone** volume (BV/TV, %): BV/TV.times.100.

DETD [0349] 5. Trabecular **bone** number (TBN, #/mm): 1.199/2.times.BS/TV.

DETD [0350] 6. Trabecular **bone** thickness (TBT, .mu.m): (2000/1.199).times.(BV/BS).

DETD [0351] 7. Trabecular **bone** separation (TBS, .mu.m): (2000.times.1.199).times.(TV-BV).

DETD [0352] II. Measurements and calculations related to **bone** resorption

DETD [0353] 1. **Osteoclast** number (OCN, #): total number of **osteocdast** within total metaphyseal area.

DETD [0354] 2. **Osteoclast** perimeter (OCP, mm): length of trabecular perimeter covered by **osteoclast**.

DETD [0355] 3. **Osteoclast** number/mm (OCN/mm, #/mm): OCN/BS.

DETD [0356] 4. Percent **osteoclast** perimeter (% OCP, %): OCP/BS.times.100.

DETD [0357] III. Measurements and calculations related to **bone** formation and turnover

DETD [0363] 6. **Bone** formation rate/surface ref. (BFR/BS, .mu.m.sup.2/d/.mu.m): (SLS/2+DLS).times.MAR/BS.

DETD [0364] 7. **Bone** turnover rate (BTR, %/y): (SLS/2+DLS).times.MAR/BV.times.100.

DETD [0367] Estrogen agonist/antagonists are a class of compounds which inhibits **bone** turnover and prevents estrogen deficiency induced **bone** loss. The ovariectomized rat **bone** loss model has been widely used as a model of postmenopausal **bone** loss. Using this model, one can test the efficacy of the estrogen agonist/antagonist compounds in preventing **bone** loss and inhibiting **bone** resorption.

DETD . . . p.o.) for a certain period (such as 4 weeks). AlI rats are given subcutaneous injections of 10 mg/kg calcein (fluorochrome **bone** marker) 12 and 2 days before being sacrificed in order to examine the dynamic changes in **bone** tissue. After 4 weeks of treatment, the rats are autopsied. The following endpoints are determined:

DETD [0376] Femoral **Bone** Mineral Measurements

DETD . . . is 5.08.times.1.902 cm, resolution is 0.0254.times.0.0127 cm and scan speed is 7.25 mm/second. The femoral scan images are analyzed and **bone** area, **bone** mineral content (BMC), and **bone** mineral density (BMD) of whole femora (WF), distal femoral metaphyses (DFM), femoral shaft (FS), and proximal femora (PF) is determined

DETD [0378] Proximal Tibial Metaphyseal Cancellous **Bone** Histomorphometric Analyses

DETD . . . using Reicher-Jung Polycut S microtome. One 4 .mu.m and one 10 .mu.m sections from each rat are used for cancellous **bone** histomorphometry. The 4 .mu.m sections are stained with modified Masson's Trichrome stain while the 10 .mu.m sections remained unstained.

DETD . . . in order to restrict measurements to the secondary spongiosa The 4 .mu.m sections are used to determine indices related to **bone** volume, **bone** structure, and **bone** resorption, while the 10 .mu.m sections are used to determine indices related to **bone** formation and **bone** turnover.

DETD [0381] I. Measurements and calculations related to trabecular **bone** volume and structure

DETD [0383] 2. Trabecular **bone** area (BV, mm.sup.2): total area of trabeculae within TV.

DETD [0384] 3. Trabecular **bone** perimeter (BS, mm): the length of total perimeter of trabeculae.

DETD [0385] 4. Trabecular **bone** volume (BV/TV, %): BV/TV.times.100.

DETD [0386] 5. Trabecular **bone** number (TBN, #/mm): 1.199/2 .times.BS/TV.

DETD [0387] 6. Trabecular **bone** thickness (TBT, .mu.m): (2000/1.199).times.(BV/BS).

DETD [0388] 7. Trabecular **bone** separation (TBS, .mu.m): (2000.times.1.199).times.(TV-BV).

DETD [0389] II. Measurements and calculations related to **bone** resorption

DETD [0390] 1. **Osteoclast** number (OCN, #): total number of **osteoclast** within total metaphyseal area

DETD [0391] 2. **Osteoclast** perimeter (OCP, mm): length of trabecular perimeter covered by **osteoclast**.

DETD [0392] 3. **Osteoclast** number/mm (OCN/mm, #/mm): OCN/BS.

DETD [0393] 4. Percent **osteoclast** perimeter (% OCP, %): OCP/BS.times.100.

DETD [0394] Ill. Measurements and calculations related to **bone** formation and turnover

DETD [0399] 6. **Bone** formation rate/surface ref. (BFR/BS, .mu.m.sup.2/d/.mu.m): (SLS/2+DLS).times.MAR/BS.

DETD [0400] 7. **Bone** turnover rate (BTR, %/y): (SLS/2+DLS).times.MAR/BV.times.100.

DETD [0403] The activity of anabolic **bone** agents in stimulating **bone** formation and increasing **bone** mass can be tested in intact male or female rats, sex hormone deficient male (orchidectomy) or female (ovariectomy) rats.

DETD . . . 2 months). In the castrated rats, treatment is started at the next day after surgery (for the purpose of preventing **bone** loss) or at the time **bone** loss has already occurred (for the purpose of restoring **bone** mass). During the study, all rats are allowed free access to water and a pelleted commercial diet (Teklad Rodent Diet. . .

DETD [0406] Femoral **Bone** Mineral Measurements

DETD . . . is 5.08.times.1.902 cm, resolution is 0.0254.times.0.0127 cm and scan speed is 7.25 mm/second. The femoral scan images are analyzed and **bone** area. **bone** mineral content (BMC), and **bone** mineral density (BMD) of whole femora (WF), distal femoral metaphyses PFM), femoral shaft (FS), and proximal femora (PF) are determined

DETD [0408] Proximal Tibial Metaphvseal Cancellous **Bone** Histomorphometric Analyses

DETD . . . using Relchert-Jung Polycut S microtome. One 4 .mu.m and one 10 .mu.m sections from each rat are used for cancellous **bone** histomorphometry. The 4 .mu.m sections are stained with modified Masson's Trichrome stain while the 10 .mu.m sections remained unstained.

DETD . . . in order to restrict measurements to the secondary spongiosa. The 4 .mu.m sections are used to determine indices related to **bone** volume, **bone** structure, and **bone** resorption, while the 10 .mu.m sections are used to determine indices related to **bone** formation and **bone** turnover.

DETD [0411] I. Measurements and calculations related to trabecular **bone** volume and stricture

DETD [0413] 2. Trabecular **bone** area (BV, mm.sup.2: total area of trabeculae within TV.

DETD [0414] 3. Trabecular **bone** perimeter (BS, mm): the length of total perimeter of trabeculae.

DETD [0415] 4. Trabecular **bone** volume (BV/TV, %): BV/TV.times.100.

DETD [0416] 5. Trabecular **bone** number (TBN, #/mm): 1.199/2.times.BS/TV.

DETD [0417] 6. Trabecular **bone** thickness (TBT, .mu.m): (2000/1.199).times.(BV/BS).

DETD [0418] 7. Trabecular **bone** separation (TBS, .mu.m): (2000.times.1.199).times.(TV-BV).

DETD [0419] II. Measurements and calculations related to **bone** resorption

DETD [0420] 1. **Osteoclast** number (OCN, #): total number of **osteoclast** within total metaphyseal area.

DETD [0421] 2. **Osteoclast** perimeter (OCP, mm): length of trabecular perimeter covered by **osteociast**.

DETD [0422] 3. **Osteoclast** number/mm (OCN/mm, #/mm): OCN/BS.

DETD [0423] 4. Percent **osteoclast** perimeter (% OCP, %): OCP/BS.times.100.

DETD [0424] III. Measurements and calculations related to **bone** formation and turnover

DETD [0430] 6. **Bone** formation rate/surface ref. (BF/RIBS, .mu.m.sup.2/d/.mu.m): (SLS/2+DLS).times.MAR/BS.

DETD [0431] 7. **Bone** turnover rate (BTR, %/y): (SLS/2+DLS).times.MAR/BV.times.100.

DETD [0446] For example, the **bone** anabolic agent can be used alone or in combination with an antiresorptive agent for three months to three years, followed. . . agent alone for three months to three years, with optional repeat of the full treatment cycle. Alternatively, for example, the **bone** anabolic agent can be used alone or in combination with an anti-resorptive agent for three months to three years, followed. . . second compound as described above (e.g., PGE.sub.2) may be administered once daily for a period of time sufficient to augment **bone** mass to a level which is above the **bone fracture** threshold (World Health Organization Study "Assessment of **Fracture** Risk and its Application to Screening for Postmenopausal **Osteoporosis** (1994). Report of a World Health Organization Study Group. World Health Organization Technical Series 843") followed by administration of a. . .

DETD . . . dosages given below are a guideline and the physician may titrate doses of the drug to achieve the activity (e.g., **bone** mass augmentation) that the physician considers appropriate for the individual patient. In considering the degree of activity desired, the physician must balance a variety of factors such as **bone** mass starting level, age of the patient, presence of preexisting disease, as well as presence of other diseases (e.g., cardiovascular).. . .

DETD [0448] The amount of the antresorptive agent to be used is determined by its activity as a **bone** loss inhibiting agent. This activity is determined by means of an individual compound's pharmacokinetics and its minimal maximal effective dose in inhibition of **bone** loss using a protocol as described above (ESTROGEN AGONIST/ANTAGONIST PROTOCOL).

DETD [0449] In general an effective dosage for the activities of this invention, for example the **bone** resorption activities of this invention, for the first compounds of this invention is in the range of 0.01 to 200. . .

DETD [0463] In general an amount of a **bone** anabolic agent (e.g., PGE.sub.2) is used that is sufficient to augment **bone** mass to a level which is above the **bone fracture** threshold (as detailed in the World Health Organization Study previously cited herein).

DETD [0464] In general an effective dosage for the **bone** anabolic agent described above is in the range of 0.001 to 100 mg/kg/day, preferably 0.1 to 10 mg/kg/day.

DETD [0476] Since the present invention relates to the augmentation and maintenance of **bone** mass by treatment with a combination of active ingredients which may be administered separately, the invention also relates to combining. . .

DETD . . . tablet or capsule or several pills or capsules to be taken on a given day. Also a daily dose of **bone** anabolic agent can consist of one tablet or capsule while a daily dose of a anti-resorptive

agent can consist of. . .

DETD . . . ovariectomized (OVX) at month 0. Three months post-surgery, OVX rats were treated with either Prostaglandin E.sub.2 (PGE.sub.2), a known anabolic **bone** agent, at 3 mg/kg/day (subcutaneously injection), or PGE.sub.2 at 3 mg/kg/day (subcutaneously injection) combined with droloxifene (DRO) at 10 mg/kg/day. . .

DETD [0495] Lumbar Vertebral **Bone** Mineral Measurements

DETD . . . Inc., Waltham, Mass.) equipped with a "Regional High Resolution Scan" software (Hologic, Inc., Waltham, Mass.) was used to determined the **bone** area, **bone** mineral content (BMC), and **bone** mineral density (BMD) of whole lumbar spine and each of the six lumbar vertebrae (LV1-6) in the anesthetized rats. The. . . resolution was 0.0254.times.0.0127 cm, and scan speed was 7.25 mm/sec. The whole lumbar spine scan image was obtained and analyzed. **Bone** area (BA), and **bone** mineral content (BMC) were determined, and **bone** mineral density was calculated (MBC divided by BA) for the whole lumbar spine and each of the six lumbar vertebrae. . .

DETD . . . observed. On the other hand, when DRO treatment was given to these OVX rats after discontinuation of PGE.sub.2, the PGE.sub.2-restored **bone** was completely maintained. Similarly, discontinuation of both PGE.sub.2 and DRO for 1.5 months produced a significant decrease in BMD of LV3. However, when PGE.sub.2 was withdrawn and DRO treatment was continued for another 1.5 months, no **bone** loss was found in the lumbar spine of these OVX rats. We concluded that DRO, an anti-resorptive agent, did not blunt the anabolic effects of PGE.sub.2 in **osteogenic** rats. Further, DRO was efficacious in maintaining PGE.sub.2-restored **bone** after discontinuation of PGE.sub.2. These data support the strategy of using an anabolic agent to restore **bone** mass in the **osteoporotic** skeleton followed by an anti-resorptive agent to maintain the restored **bone** mass.

CLM What is claimed is:

11. A method for treating a mammal having a condition which presents with low **bone** mass comprising administering to a mammal having a condition which presents with low **bone** mass a. a therapeutically effective amount of a first compound, said first compound being an estrogen agonist/antagonist; and b. a. . .

17. A method as recited in claim 14 wherein the condition which presents with low **bone** mass is **osteoporosis**.

21. A method as recited in claim 18 wherein the condition which presents with low **bone** mass is **osteoporosis**.

30. A method for treating mammals which present with low **bone** mass comprising administering to a mammal having a condition which presents with low **bone** mass the pharmaceutical composition of claim 1.

. . . first compound alone and the amount of the second compound alone is insufficient to achieve therapeutic effects of increase in **bone** formation and decrease in **bone** resorption if administered simultaneously and wherein the combined effect of the amount of the first and second compounds is greater. . .

32. A method for treating a mammal having a condition which presents with low **bone** mass comprising administering to a mammal having a condition which presents with low **bone** mass a. an amount of a first compound, said first compound being an estrogen agonist/antagonist; and b. an amount of. . . compound alone and the amount of the second compound alone is insufficient to achieve the therapeutic effects of increase in **bone** formation and decrease in **bone** resorption if administered simultaneously and wherein the combined effect of the amounts of the first and second compounds is

greater. . .
33. A kit containing a treatment for a condition which presents with low **bone** mass comprising: a. a therapeutically effective amount of an estrogen agonist/antagonist and a pharmaceutically acceptable carrier in a first unit. . .
. . . or idoxifene; and b. a therapeutically effective amount of a second compound, said second compound being sodium fluoride or N-[1(R)-[1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide: **MK-677**.

36. A method for treating a mammal having a condition which presents with low **bone** mass comprising administering to a mammal having a condition which presents with low **bone** mass a. a therapeutically effective amount of a first compound, said first compound being droloxifene, raloxifene, tamoxifen or idoxifene; and b. a therapeutically effective amount of a second compound, said second compound being sodium fluoride or N-[1(R)-[1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide:**MK-677**.

37. A method as recited in claim 36 wherein the condition which presents with low **bone** mass is **osteoporosis.**

42. A method for treating mammals which present with low **bone** mass comprising administering to a mammal having a condition which presents with low **bone** mass the pharmaceutical composition of claim 34.

. . . droloxifene, raloxifene, tamoxifen or idoxifene; and b. an amount of a second compound, said second compound being sodium fluoride or N-[1(R)-[1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-methylpropanamide:**MK-677** wherein the amount of the first compound alone and the amount of the second compound alone is insufficient to achieve the therapeutic effects of increase in **bone** formation and decrease in **bone** resorption if administered simultaneously and wherein the combined effect of the amounts of the first and second compounds is greater. . .
44. A method for treating a mammal having a condition which presents with low **bone** mass comprising administering to a mammal having a condition which presents with low **bone** mass a. an amount of a first compound, said first compound being droloxifene, raloxifene, tamoxifen or idoxifene; and b. an. . . compound alone and the amount of the second compound alone is insufficient to achieve the therapeutic effects of increase in **bone** formation and decrease in **bone** resorption if administered simultaneously and wherein the combined effect of the amounts of the first and second compounds is greater. . .
45. A kit containing a treatment for a condition which presents with low **bone** mass comprising: a. a therapeutically effective amount of droloxifene, raloxifene, tamoxifen or idoxifene and a pharmaceutically acceptable carrier in a first unit dosage form; b. a therapeutically effective amount of a sodium fluoride or N-[1(R)-[1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide:**MK-677** and a pharmaceutically acceptable carrier in a second unit dosage form; and c. container means for containing said first and. .

52. A method for treating a mammal having a condition which presents with low **bone** mass comprising administering to a mammal having a condition which presents with low **bone** mass a. a

therapeutically effective amount of a first compound, said first compound being Cis-6-(4-fluoro-phenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydronaphthaiene-2-ol; (-)-Cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydronaphthalene-2-ol; Cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydronaphthalene-2-ol; Cis-1-[6'-pyrrolodinoethoxy-3'-pyridyl]2-phenyl-6-hydroxy-1,2,3,4-tetrahydrohaphthalene; 1-(4'-Pyrrolidinoethoxyphenyl)-2-(4"-fluorophenyl)-6-hydroxy-1,2,3,4-tetrahydroisoquinoline; Cis-6-(4-hydroxyphenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydronaphthalene2-ol. . .
57. A method as recited in claim 52 wherein the condition which presents with low **bone** mass is **osteoporosis**.

62. A method for treating mammals which present with low **bone** mass comprising administering to a mammal having a condition which presents with low **bone** mass the pharmaceutical composition of claim 46.

. . . compound alone and the amount of the second compound alone is insufficient to achieve the therapeutic effects of increase in **bone** formation and decrease in **bone** resorption if administered simultaneously and wherein the combined effect of the amounts of the first and second compounds is greater. . .
64. A method for treating a mammal having a condition which presents with low **bone** mass comprising administering to a mammal having a condition which presents with low **bone** mass a. an amount of a first compound, said first compound being Cis-6-(4-fluoro-phenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydronaphthalene-2-ol; (-)-Cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydronaphthalene-2-ol; Cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydronaphthalene-2; Cis-1-[6'-pyrrolodinoethoxy-3'-pyridyl -2-phenyl]-6-hydroxy-1,2,3,4-tetrahydrohaphthalene; 1-(4'-Pyrrolidinoethoxyphenyl)-2-(4"-fluorophenyl)-6-hydroxy-1,2,3,4-tetrahydroisoquinoline; Cis-6-(4-hydroxyphenyl)-5-[4-(2-piperidin-1-yl-ethoxy)phenyl]-5,6,7,8-tetrahydronaphthalene-2-ol; or. . . compound alone and the amount of the second compound alone is insufficient to achieve the therapeutic effects of increase in **bone** formation and decrease in **bone** resorption if administered simultaneously and wherein the combined effect of the amounts of the first and second compounds is greater. . .
65. A kit containing a treatment for a condition which presents with low **bone** mass comprising: a. a therapeutically effective amount of Cis-6-(4-fluoro-phenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydronaphthalene-2-ol; (-)-Cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydronaphthalene2ol; Cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydronaphthalene-2-ol; Cis-1-[6'-pyrrolodinoethoxy-3'-pyridyl]-2-phenyl-6-hydroxy-1,2,3,4-tetrahydrohaphthalene; 1-(4'-Pyrrolidinoethoxyphenyl)-2-(4"-fluorophenyl)-6-hydroxy-1,2,3,4-tetrahydroisoquinoline; Cis-6-(4-hydroxyphenyl)-5-[4-(2-piperidin 1-yl-ethoxy)phenyl]-5,6,7,8-tetrahydronaphthaiene2-ol; or 1-(4'-Pyrrolidinolethoxyphenyl)-2-phenyl-6-hydroxy-1,2,3,4-tetrahydroisoquinoline and a pharmaceutically. . .
79. A method for treating a mammal having a condition which presents with low **bone** mass comprising administering to a mammal having a condition which presents with low **bone** mass a. a therapeutically effective amount of a first compound, said first compound being raloxifene, tamoxifen or idoxifene; and b.. . .
84. A method as recited in claim 79 wherein the condition which presents with low **bone** mass is **osteoporosis**.

89. A method for treating mammals which present with low **bone** mass comprising administering to a mammal having a condition which

presents with low **bone** mass the pharmaceutical composition of claim 73.

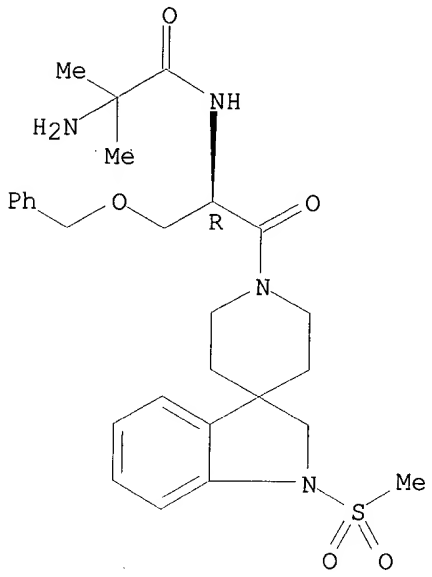
. . . compound alone and the amount of the second compound alone is insufficient to achieve the therapeutic effects of increase in **bone** formation and decrease in **bone** resorption if administered simultaneously and wherein the combined effect of the amounts of the first and second compounds is greater. . .
91. A method for treating a mammal having a condition which presents with low **bone** mass comprising administering to a mammal having a condition which presents with low **bone** mass a. an amount of a first compound, said first compound being raloxifene, tamoxifen or idoxifene; and b. an amount. . . compound alone and the amount of the second compound alone is insufficient to achieve the therapeutic effects of increase in **bone** formation and decrease in **bone** resorption if administered simultaneously and wherein the combined effect of the amounts of the first and second compounds is greater. . .
92. A kit containing a treatment for a condition which presents with low **bone** mass comprising: a. a therapeutically effective amount of raloxifene, tamoxifen or idoxifene; and a pharmaceutically acceptable carrier in a first. . .

IT **Bone diseases**
IT **Bone formation**
IT **Bone resorption inhibitors**
IT Drug delivery systems
IT **Osteoporosis**
IT Synergistic drug interactions
(estrogen agonists/antagonists and prostaglandins or prostaglandin agonists/antagonists as combination therapy for bone disorders including osteoporosis)
IT 363-24-6, PGE2 551-11-1, PGF2.alpha. 745-65-3, PGE1 7681-49-4, Sodium fluoride, biological studies 9002-64-6, Parathyroid hormone 10540-29-1, Tamoxifen 17968-82-0, PGD1 31477-60-8, Centchroman 41598-07-6, PGD2 68047-06-3, 4-Hydroxytamoxifen 82413-20-5, Droloxifene 84449-90-1, Raloxifene 116057-75-1, Idoxifene 123123-44-4 **159752-10-0**, MK-677 180915-78-0 180915-84-8 180915-86-0 180916-14-7 180916-15-8 180916-16-9 193274-89-4 195962-24-4
(estrogen agonists/antagonists and prostaglandins or prostaglandin agonists/antagonists as combination therapy for bone disorders including osteoporosis)
IT **159752-10-0**, MK-677
(estrogen agonists/antagonists and prostaglandins or prostaglandin agonists/antagonists as combination therapy for bone disorders including osteoporosis)
RN 159752-10-0 USPATFULL
CN Propanamide, 2-amino-N-[(1R)-2-[1,2-dihydro-1-(methylsulfonyl)spiro[3H-indole-3,4'-piperidin]-1'-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl-, monomethanesulfonate (9CI) (CA INDEX NAME)

CM 1

CRN 159634-47-6
CMF C27 H36 N4 O5 S
CDES 1:R

Absolute stereochemistry.



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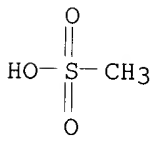

L73 ANSWER 6 OF 10 USPATFULL on STN
AN 2001:82525 USPATFULL
TI Assays for growth hormone secretagogue receptors
IN Pai, Lee-Yuh, Westfield, NJ, United States
Feighner, Scott D., Highlands, NJ, United States
Howard, Andrew D., Park Ridge, NJ, United States
Pong, Sheng-Shung, Edison, NJ, United States
Van Der Ploeg, Leonardus H. T., Scotch Plains, NJ, United States
PA Merck & Co., Inc., Rahway, NJ, United States (U.S. corporation)
PI US 6242199 B1 20010605
WO 9722004 19970619
AI US 1998-77675 19980603 (9)
WO 1996-US19442 19961210
19980603 PCT 371 date
19980603 PCT 102(e) date
PRAI US 1995-8582P 19951213 (60) <--
DT Utility
FS Granted
EXNAM Primary Examiner: Kemmerer, Elizabeth; Assistant Examiner: Kaufman, Claire M.
LREP Cocuzzo, Anna L., Tribble, Jack L.
CLMN Number of Claims: 8
ECL Exemplary Claim: 2
DRWN 39 Drawing Figure(s); 34 Drawing Page(s)
LN.CNT 1142

193272-29-6P 193272-30-9P 193272-31-0P 193272-32-1P 193272-33-2P
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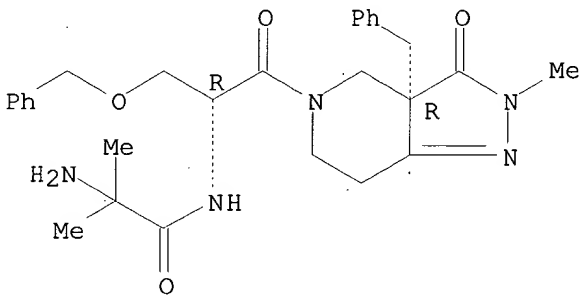
193273-84-6P 193273-85-7P 193273-86-8P 193273-87-9P 193273-88-0P
(prepn. of nitrogen heterocyclic peptide analogs as growth-hormone secretagogues)

IT **193270-49-4P 193273-65-3P 193273-66-4P**
193273-67-5P 193273-68-6P 193273-69-7P
(prepn. of nitrogen heterocyclic peptide analogs as growth-hormone secretagogues)

RN 193270-49-4 USPATFULL

CN Propanamide, 2-amino-N-[(1R)-2-[(3aR)-2,3,3a,4,6,7-hexahydro-2-methyl-3-oxo-3a-(phenylmethyl)-5H-pyrazolo[4,3-c]pyridin-5-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

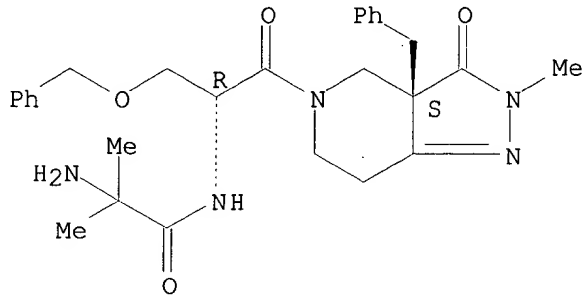


● HCl

RN 193273-65-3 USPATFULL

CN Propanamide, 2-amino-N-[(1R)-2-[(3aS)-2,3,3a,4,6,7-hexahydro-2-methyl-3-oxo-3a-(phenylmethyl)-5H-pyrazolo[4,3-c]pyridin-5-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl-, monohydrochloride (9CI) (CA INDEX NAME)

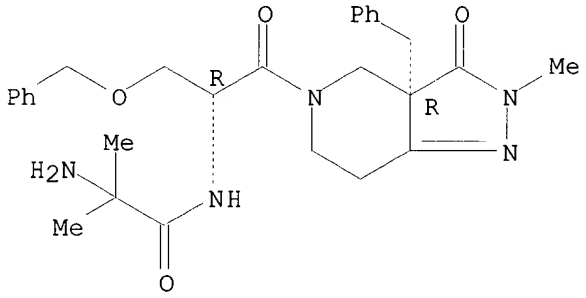
Absolute stereochemistry.



● HCl

RN 193273-66-4 USPATFULL
CN Propanamide, 2-amino-N-[(1R)-2-[(3aR)-2,3,3a,4,6,7-hexahydro-2-methyl-3-oxo-3a-(phenylmethyl)-5H-pyrazolo[4,3-c]pyridin-5-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

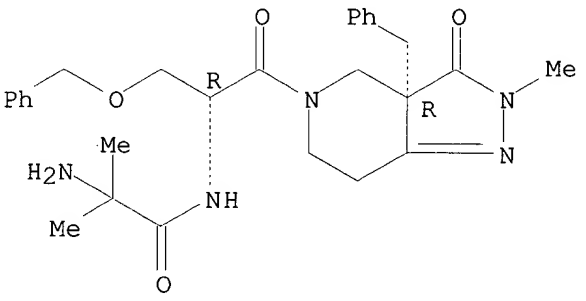


RN 193273-67-5 USPATFULL
CN Propanamide, 2-amino-N-[(1R)-2-[(3aR)-2,3,3a,4,6,7-hexahydro-2-methyl-3-oxo-3a-(phenylmethyl)-5H-pyrazolo[4,3-c]pyridin-5-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl-, monomethanesulfonate (9CI) (CA INDEX NAME)

CM 1

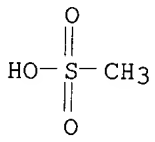
CRN 193273-66-4
CMF C28 H35 N5 O4

Absolute stereochemistry.



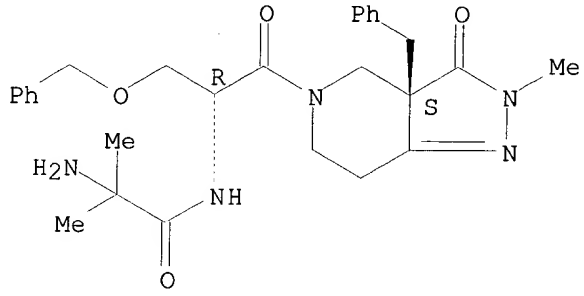
CM 2

CRN 75-75-2
CMF C H4 O3 S



RN 193273-68-6 USPATFULL
CN Propanamide, 2-amino-N-[(1R)-2-[(3aS)-2,3,3a,4,6,7-hexahydro-2-methyl-3-oxo-3a-(phenylmethyl)-5H-pyrazolo[4,3-c]pyridin-5-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

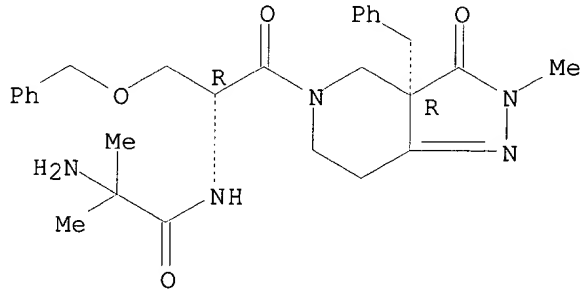


RN 193273-69-7 USPATFULL
CN Propanamide, 2-amino-N-[(1R)-2-[(3aR)-2,3,3a,4,6,7-hexahydro-2-methyl-3-oxo-3a-(phenylmethyl)-5H-pyrazolo[4,3-c]pyridin-5-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl-, (2R,3R)-2,3-dihydroxybutanedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 193273-66-4
CMF C28 H35 N5 O4

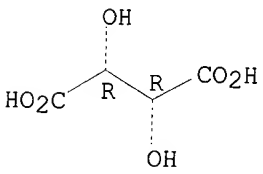
Absolute stereochemistry.



CM 2

CRN 87-69-4
CMF C4 H6 O6
CDES 1:R2:R*,R*

Absolute stereochemistry.



L73 ANSWER 8 OF 10 USPATFULL on STN
AN 2000:109811 USPATFULL
TI Heterocyclic compounds
IN Carpino, Philip A, Groton, CT, United States
DaSilva-Jardine, Paul A, Providence, RI, United States
Lefker, Bruce A, Gales Ferry, CT, United States
Ragan, John A, Gales Ferry, CT, United States
PA **Pfizer Inc.**, New York, NY, United States (U.S. corporation)
PI US 6107306 20000822
AI US 1999-259691 19990301 (9)
RLI Division of Ser. No. US 68566
PRAI US 1995-9469P 19951228 (60) <--
DT Utility
FS Granted
EXNAM Primary Examiner: Dentz, Bernard
LREP Richardson, Peter C., Benson, Gregg C., Ronau, Robert T.
CLMN Number of Claims: 87
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 4701
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention is directed to compounds of the formula ##STR1## and the pharmaceutically-acceptable salts thereof, where the substituents are as defined in the Specification, which are growth hormone secretogogues and which increase the level of endogenous growth hormone. The compounds of this invention are useful for the treatment and prevention of **osteoporosis**, congestive heart failure, frailty associated with aging, obesity; accelerating **bone fracture** repair, attenuating protein catabolic response after a major operation, reducing cachexia and protein loss due to chronic illness, accelerating wound healing, or accelerating the recovery of burn patients or patients having undergone major surgery; improving muscle strength, mobility, maintanence of skin thickness, metabolic homeostasis or renal homeostasis. The compounds of the present invention are also useful in treating **osteoporosis** when used in combination with: a bisphosphonate compound such as alendronate; estrogen, premarin, and optionally progesterone; an estrogen agonist or antagonist; or calcitonin, and pharmaceutical compositions useful therefor. Further, the present invention is directed to pharmaceutical compositions useful for increasing the endogenous production or release of growth hormone in a human or other animal which comprises an effective amount of a compound of the present invention and a growth hormone secretagogue selected from GHRP-6, Hexarelin, GHRP-1, growth hormone releasing factor (GRF), IGF-1, IGF-2 or B-HT920. The invention is also directed to intermediates useful in the preparation of compounds of formula I.
PA **Pfizer Inc.**, New York, NY, United States (U.S. corporation)
PRAI US 1995-9469P 19951228 (60) <--
AB . . . increase the level of endogenous growth hormone. The compounds

of this invention are useful for the treatment and prevention of **osteoporosis**, congestive heart failure, frailty associated with aging, obesity; accelerating **bone fracture** repair, attenuating protein catabolic response after a major operation, reducing cachexia and protein loss due to chronic illness, accelerating wound. . . maintanence of skin thickness, metabolic homeostasis or renal homeostasis. The compounds of the present invention are also useful in treating **osteoporosis** when used in combination with: a bisphosphonate compound such as alendronate; estrogen, premarin, and optionally progesterone; an estrogen agonist or. . .

SUMM This invention relates to dipeptide compounds which are growth hormone secretagogues and are useful for the treatment and prevention of **osteoporosis**.

SUMM . . . the truncal region. Decreased skeletal and cardiac muscle mass and muscle strength lead to a significant reduction in exercise capacity. **Bone** density is also reduced. Administration of exogenous growth hormone has been shown to reverse many of the metabolic changes. Additional. . .

SUMM The compounds of WO 94/11012 and WO 94/13696 are reported to be useful in the treatment of **osteoporosis** in combination with parathyroid hormone or a bisphosphonate.

SUMM a method for the treatment or prevention of **osteoporosis** which comprises administering to a human or other animal in need of such treatment or prevention an amount of a compound of Formula I which is effective in treating or preventing **osteoporosis**;

SUMM a method for the treatment or prevention of **osteoporosis** which comprises administering to a human or other animal with **osteoporosis** a combination of a bisphosphonate compound such as alendronate, and especially preferred is the bisphosphonate compound ibandronate, and a compound. . .

SUMM a method for the treatment or prevention of **osteoporosis** which comprises administering to a human or other animal with **osteoporosis** a combination of estrogen or Premarin.RTM. and a compound of Formula I and optionally progesterone;

SUMM a method for the treatment of **osteoporosis** which comprises administering to a human or other animal with **osteoporosis** a combination of an estrogen agonist or antagonist such as tamoxifen, droloxifene, raloxifene and idoxifene and a compound of Formula. . .

SUMM a particularly preferred method for the treatment of **osteoporosis** comprises administering to a human or other animal with **osteoporosis** a combination of an estrogen agonist or antagonist such as Cis-6-(4-fluoro-phenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol;

SUMM a method for the treatment of **osteoporosis** which comprises administering to a human or other animal with **osteoporosis** a combination of calcitonin and a compound of Formula I;

SUMM In another aspect, this invention provides methods for accelerating **bone fracture** repair, attenuating protein catabolic response after a major operation, reducing cachexia and protein loss due to chronic illness such as. . . effective in promoting release of endogenous growth hormone; of the instant method a preferred method of use is to accelerate **bone fracture** repair or for accelerating the recovery of patients having undergone major surgery.

SUMM . . . efficiency of animals raised for meat production to improve carcass quality; to increase milk production in dairy cattle; improvement of **bone** or wound healing and improvement in vital organ function. The compounds of the present invention by inducing endogenous GH secretion. . .

SUMM . . . Formula I or another compound which exhibits a different activity, e.g., an antibiotic growth permittant or an agent to treat **osteoporosis** or with other pharmaceutically active materials wherein the combination enhances efficacy and minimizes side effects.

SUMM . . . follows: stimulating growth hormone release in elderly humans;

treating growth hormone deficient adults; preventing catabolic side effects of glucocorticoids, treating **osteoporosis**, stimulating the immune system, acceleration of wound healing, accelerating **bone fracture** repair, treating growth retardation, treating congestive heart failure as disclosed in PCT publications WO 95/28173 and WO 95/28174 (and example. . . as gastrointestinal surgery; treating intrauterine growth retardation, skeletal dysplasia, hypercortisonism and Cushings syndrome; replacing growth hormone in stressed patients; treating **osteochondrodysplasias**, Noonans syndrome, sleep disorders, Alzheimer's disease, delayed wound healing, and psychosocial deprivation; treating of pulmonary dysfunction and ventilator dependency; attenuating. . . improving muscle strength, increasing muscle mass, mobility, maintenance of skin thickness, metabolic homeostasis, renal hemeostasis in the frail elderly; stimulating **osteoblasts**, **bone** remodelling, and cartilage growth; treating neurological diseases such as peripheral and drug induced neuropathy, Guillian-Barre Syndrome, amyotrophic lateral sclerosis, multiple. . .

SUMM . . . one times the dose levels which are effective when these compounds and secretagogues are used singly. Combined therapy to inhibit **bone** resorption, prevent **osteoporosis**, reduce skeletal **fracture**, enhance the healing of **bone fractures**, stimulate **bone** formation and increase **bone** mineral density can be effectuated by combinations of bisphosphonates and the growth hormone secretagogues of this invention, see PCT publication. . . The use of bisphosphonates for these utilities has been reviewed, for example, by Hamdy, N.A.T., Role of Bisphosphonates in Metabolic **Bone** Diseases, Trends in Endocrinol. Metab., 1993, 4, pages 19-25. Bisphosphonates with these utilities include but are not limited to alendronate,. . . invention of between 0.01 mg/kg to 20 mg/kg of body weight are administered to patients to obtain effective treatment of **osteoporosis**.

SUMM . . . the second compound of this invention. The term estrogen agonist/antagonist refers to compounds which bind with the estrogen receptor, inhibit **bone** turnover and prevent **bone** loss. In particular, estrogen agonists are herein defined as chemical compounds capable of binding to the estrogen receptor sites in. . . activities are readily determined by those skilled in the art according to standard assays including estrogen receptor binding assays, standard **bone** histomorphometric and densitometer methods (see Eriksen E. F. et al., **Bone** Histomorphometry, Raven Press, New York, 1994, pages 1-74; Grier S. J. et. al., The Use of Dual-Energy X-Ray Absorptiometry in Animals, Inv. Radiol., 1996, 31(1):50-62; Wahner H. W. and Fogelman I., The Evaluation of **Osteoporosis**: Dual Energy X-Ray Absorptiometry in Clinical Practice., Martin Dunitz Ltd., London 1994, pages 1-296). A variety of these compounds are. . .

SUMM The amount of the anti-resorptive agent to be used is determined by its activity as a **bone** loss inhibiting agent. This activity is determined by means of an individual compound's pharmacokinetics and its minimal maximal effective dose in inhibition of **bone** loss using a protocol such as those referenced above.

SUMM In general an effective dosage for the activities of this invention, for example the treatment of **osteoporosis**, for the estrogen agonists/antagonists (when used in combination with a compound of Formula I of this invention) is in the. . .

CLM What is claimed is:

45. A method for treating or preventing **osteoporosis** which comprises administering to a human or other animal in need of such treatment or prevention an amount of a compound of claim 1 which is effective in treating or preventing **osteoporosis**.

48. A method according for accelerating **bone fracture** repair, attenuating protein catabolic response after a major operation,

reducing cachexia and protein loss due to chronic illness, accelerating wound. . .
50. A method for the treatment or prevention of **osteoporosis** which comprises administering to a human or other animal with **osteoporosis** a combination of a bisphosphonate compound and a compound of claim 1.

51. A method for the treatment of **osteoporosis** according to claim 50 wherein the bisphosphonate compound in alendronate.

52. A method for the treatment or prevention of **osteoporosis** which comprises administering to a human or other animal with **osteoporosis** a combination of estrogen or Premarin.RTM. and a compound of claim 1 and optionally progesterone.

54. A method for the treatment of **osteoporosis** which comprises administering to a human or other animal with **osteoporosis** a combination of calcitonin and a compound of claim 1.

56. A method for the treatment of **osteoporosis** which comprises administering to a human or other animal with **osteoporosis** a combination of an estrogen agonist or antagonist and a compound of claim 1.

82. A method according to claim 48 wherein the method is for accelerating **bone fracture** repair.

84. A method for the treatment of **osteoporosis** according to claim 50 wherein the bisphosphonate compound is ibandronate.

IT Aging, animal
IT Obesity
IT **Osteoporosis**
(prepn. of nitrogen heterocyclic peptide analogs as growth-hormone secretagogues)

IT 193270-46-1P 193270-47-2P **193270-49-4P** 193270-50-7P
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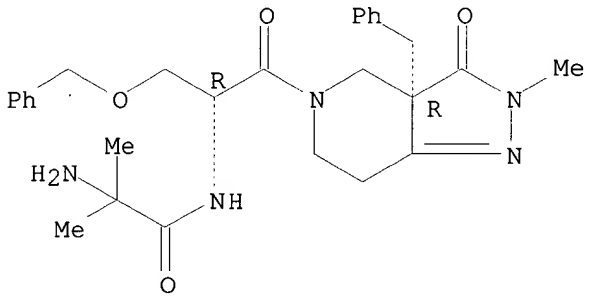
193273-84-6P 193273-85-7P 193273-86-8P 193273-87-9P 193273-88-0P
(prepn. of nitrogen heterocyclic peptide analogs as growth-hormone secretagogues)

IT **193270-49-4P 193273-65-3P 193273-66-4P**
193273-67-5P 193273-68-6P 193273-69-7P
(prepn. of nitrogen heterocyclic peptide analogs as growth-hormone secretagogues)

RN 193270-49-4 USPATFULL

CN Propanamide, 2-amino-N-[(1R)-2-[(3aR)-2,3,3a,4,6,7-hexahydro-2-methyl-3-oxo-3a-(phenylmethyl)-5H-pyrazolo[4,3-c]pyridin-5-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

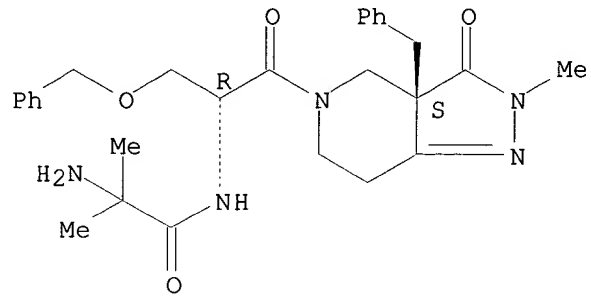


● HCl

RN 193273-65-3 USPATFULL

CN Propanamide, 2-amino-N-[(1R)-2-[(3aS)-2,3,3a,4,6,7-hexahydro-2-methyl-3-oxo-3a-(phenylmethyl)-5H-pyrazolo[4,3-c]pyridin-5-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl-, monohydrochloride (9CI) (CA INDEX NAME)

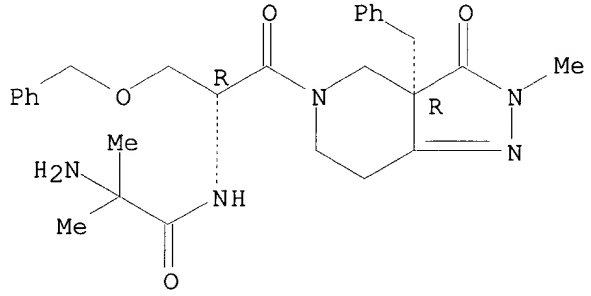
Absolute stereochemistry.



● HCl

RN 193273-66-4 USPATFULL
CN Propanamide, 2-amino-N-[(1R)-2-[(3aR)-2,3,3a,4,6,7-hexahydro-2-methyl-3-oxo-3a-(phenylmethyl)-5H-pyrazolo[4,3-c]pyridin-5-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

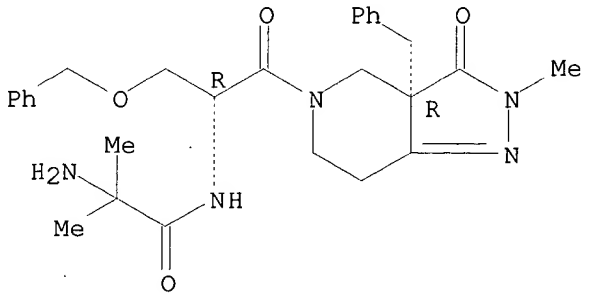


RN 193273-67-5 USPATFULL
CN Propanamide, 2-amino-N-[(1R)-2-[(3aR)-2,3,3a,4,6,7-hexahydro-2-methyl-3-oxo-3a-(phenylmethyl)-5H-pyrazolo[4,3-c]pyridin-5-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl-, monomethanesulfonate (9CI) (CA INDEX NAME)

CM 1

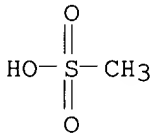
CRN 193273-66-4
CMF C28 H35 N5 O4

Absolute stereochemistry.



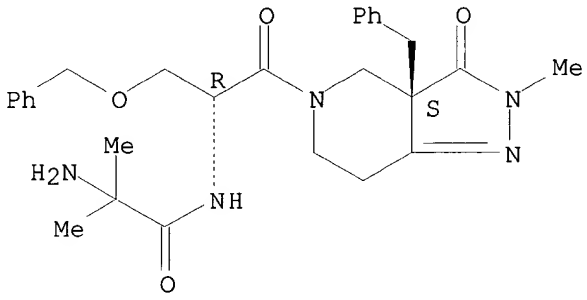
CM 2

CRN 75-75-2
CMF C H4 O3 S



RN 193273-68-6 USPATFULL
CN Propanamide, 2-amino-N-[(1R)-2-[(3aS)-2,3,3a,4,6,7-hexahydro-2-methyl-3-oxo-3a-(phenylmethyl)-5H-pyrazolo[4,3-c]pyridin-5-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

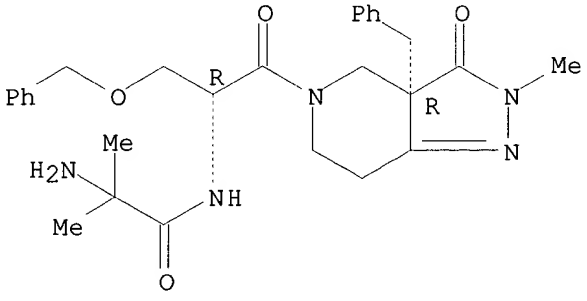


RN 193273-69-7 USPATFULL
CN Propanamide, 2-amino-N-[(1R)-2-[(3aR)-2,3,3a,4,6,7-hexahydro-2-methyl-3-oxo-3a-(phenylmethyl)-5H-pyrazolo[4,3-c]pyridin-5-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl-, (2R,3R)-2,3-dihydroxybutanedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 193273-66-4
CMF C28 H35 N5 O4

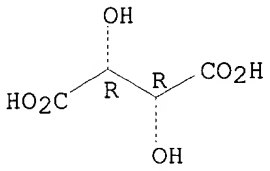
Absolute stereochemistry.



CM 2

CRN 87-69-4
CMF C4 H6 O6
CDES 1:R2:R*,R*

Absolute stereochemistry.



L73 ANSWER 9 OF 10 USPATFULL on STN
AN 1998:69042 USPATFULL
TI Polymorphic forms of a growth hormone secretagogue
IN Draper, Jerome P., Elkins Park, PA, United States
Kaufman, Michael J., New Hope, PA, United States
Dubost, David C., Collegeville, PA, United States
McCauley, James A., Belle Mead, NJ, United States
Vandrilla, Jennifer L., Cranford, NJ, United States
Varsolona, Richard J., Scotch Plains, NJ, United States
PA Merck & Co., Inc., Rahway, NJ, United States (U.S. corporation)
PI US 5767124 19980616
AI US 1996-736170 19961023 (8)
PRAI US 1995-590P 19951027 (60) <--
DT Utility
FS Granted
EXNAM Primary Examiner: Ivy, C. Warren; Assistant Examiner: Huang, Evelyn
LREP Thies, J. Eric, Rose, David L.
CLMN Number of Claims: 15
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 2228
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention is concerned with polymorphic forms of the compound N-[1(R)-[(1,2-dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide methanesulfonate which is a growth hormone secretagogue that is useful in food animals to promote their growth thereby rendering the production of edible meat products more efficient, and in humans, to treat physiological or medical conditions characterized by a deficiency in growth hormone secretion, and to treat medical conditions which are improved by the anabolic effects of growth hormone. The instant polymorphic forms have advantages over the other known forms of N-[1(R)-[(1,2-dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(phenylmethyloxy)-ethyl]-2-amino-2-methylpropanamide methanesulfonate in terms of thermodynamic stability and suitability for inclusion in pharmaceutical formulations. The present invention is also concerned with processes for preparing these polymorphic forms, pharmaceutical formulations comprising these polymorphic forms as active ingredients and the use of the polymorphic form of the compound and their formulations in the treatment of certain disorders.
PRAI US 1995-590P 19951027 (60) <--
DETD . . . present invention or another composition which exhibits a different activity, e.g., an antibiotic growth permittant or an agent to treat **osteoporosis** or in combination with a corticosteroid to minimize the catabolic side effects or with other pharmaceutically active materials wherein the. . .
DETD . . . growth hormone release in elderly humans; treating growth

hormone deficient adults; prevention of catabolic side effects of glucocorticoids; treatment of **osteoporosis**; stimulation of the immune system, acceleration of wound healing; accelerating **bone fracture** repair; treatment of growth retardation; treating acute or chronic renal failure or insufficiency; treatment of physiological short stature, including growth. . . of intrauterine growth retardation, and skeletal dysplasia, treatment of peripheral neuropathies; replacement of growth hormone in stressed patients; treatment of **osteochondrody**-splasias, Noonans syndrome, schizophrenia, depression, Alzheimer's disease, delayed wound healing, and psychosocial deprivation; treatment of pulmonary dysfunction and ventilator dependency; attenuation. . . virus; improvement in muscle strength, mobility, maintenance of skin thickness, metabolic homeostasis, renal hemeostasis in the frail elderly; stimulation of **osteoblasts**, **bone** remodelling, and cartilage growth; stimulation of the immune system in companion animals and treatment of disorders of aging in companion. . .

DETD . . . particular, the instant compounds are useful in the prevention or treatment of a condition selected from the group consisting of: **osteoporosis**; catabolic illness; immune deficiency, including that in individuals with a depressed T.sub.4 /T.sub.8 cell ratio; hip **fracture**; musculoskeletal impairment in the elderly; growth hormone deficiency in adults or in children; obesity; cachexia and protein loss due to. . .

DETD Combined therapy to inhibit **bone** resorption, prevent **osteoporosis** and enhance the healing of **bone fractures** can be illustrated by combinations of bisphosphonates and the growth hormone secretagogues of this invention. The use of bisphosphonates for these utilities has been reviewed, for example, by Hamdy, N. A. T., Role of Bisphosphonates in Metabolic **Bone** Diseases, Trends in Endocrinol. Metab., 4, 19-25 (1993). Bisphosphonates with these utilities include alendronate, tiludronate, dimethyl-APD, risedronate, etidronate, YM-175, clodronate,. . . invention of between 0.01 mg/kg to 20 mg/kg of body weight are administered to patients to obtain effective treatment of **osteoporosis**.

DETD In the case of alendronate daily oral dosage levels of 0.1 mg to 50 mg are combined for effective **osteoporosis** therapy with 0.01 mg/kg to 20 mg/kg of the growth hormone secretagogues of this invention. **Osteoporosis** and other **bone** disorders may also be treated with compounds of this invention in combination with calcitonin, estrogens, raloxifene and calcium supplements such. . .

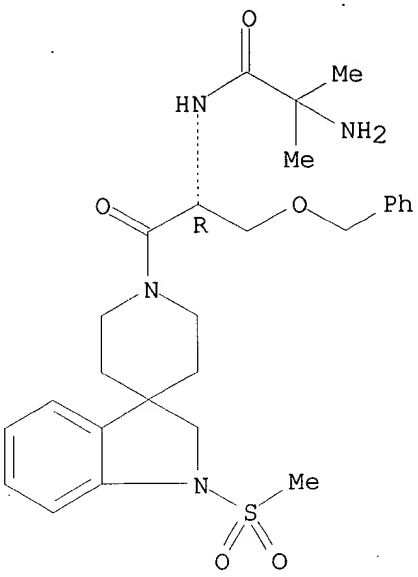
IT 10314-98-4P 10314-99-5P 138163-08-3P **159633-92-8P** **159634-47-6P** 159634-86-3P 159634-87-4P 159634-88-5P 159634-89-6P **159752-10-0P** 167484-18-6P 178261-41-1P 180465-66-1P 180465-67-2P 184289-83-6P 184289-84-7P 184289-85-8P
(prepn. of aminomethylpropanamide derivs. for the treatment of physiol. or medical conditions and certain disorders)

IT **159633-92-8P** **159634-47-6P** **159752-10-0P**
(prepn. of aminomethylpropanamide derivs. for the treatment of physiol. or medical conditions and certain disorders)

RN 159633-92-8 USPATFULL

CN Propanamide, 2-amino-N-[(1R)-2-[1,2-dihydro-1-(methylsulfonyl)spiro[3H-indole-3,4'-piperidin]-1'-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl-, monohydrochloride (9CI) (CA INDEX NAME)

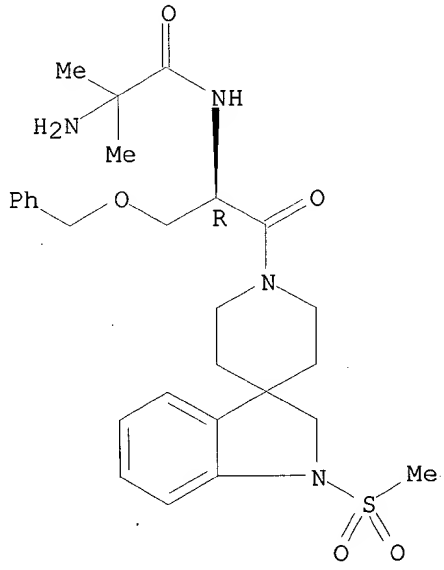
Absolute stereochemistry.



● HCl

RN 159634-47-6 USPATFULL
CN Propanamide, 2-amino-N-[(1R)-2-[1,2-dihydro-1-(methylsulfonyl)spiro[3H-indole-3,4'-piperidin]-1'-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

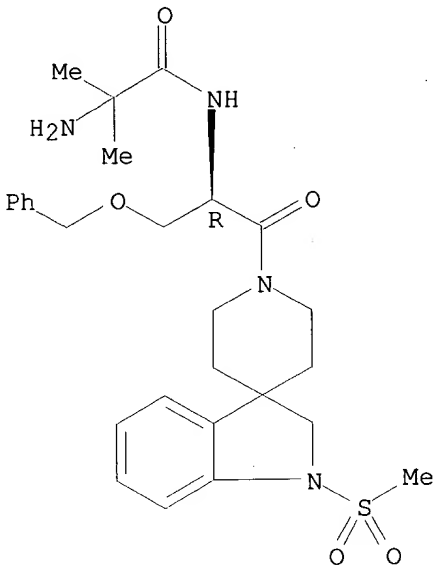


RN 159752-10-0 USPATFULL
CN Propanamide, 2-amino-N-[(1R)-2-[1,2-dihydro-1-(methylsulfonyl)spiro[3H-indole-3,4'-piperidin]-1'-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl-, monomethanesulfonate (9CI) (CA INDEX NAME)

CM 1

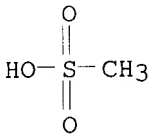
CRN 159634-47-6
CMF C27 H36 N4 O5 S
CDES 1:R

Absolute stereochemistry.



CM 2

CRN 75-75-2
CMF C H4 O3 S



L73 ANSWER 10 OF 10 USPAT2 on STN
AN 2002:92672 USPAT2
TI Growth-hormone secretagogues
IN Carpino, Philip A, Groton, CT, United States
DaSilva-Jardine, Paul A, Providence, RI, United States
Lefker, Bruce A, Gales Ferry, CT, United States
Ragan, John A, Gales Ferry, CT, United States
PA **Pfizer Inc.**, New York, NY, United States (U.S. corporation)
PI US 6482825 B2 20021119
AI US 2000-734274 20001211 (9)
RLI Continuation of Ser. No. US 68566
PRAI US 1995-9469P 19951228 (60) <--
DT Utility
FS GRANTED
EXNAM Primary Examiner: Raymond, Richard L.; Assistant Examiner: Balasubramanian, Venkataraman
LREP Richardson, Peter C., Benson, Gregg C., Wichtowski, John A.
CLMN Number of Claims: 34
ECL Exemplary Claim: 1
DRWN 0 Drawing Figure(s); 0 Drawing Page(s)
LN.CNT 4099
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention provides compounds of formula I ##STR1##

and pharmaceutically-acceptable salts thereof, where the substituents are defined in the specification, which are growth hormone secretogogues useful for treatment and prevention of **osteoporosis**, congestive heart failure, frailty associated with aging, obesity; accelerating **bone fracture** repair, attenuating protein catabolic response after a major operation, reducing cachexia and protein loss due to chronic illness, accelerating wound healing, or accelerating the recovery of burn patients or patients having undergone major surgery; improving muscle strength , mobility, maintenance of skin thickness, metabolic homeostatis or renal homeostasis. Compounds of formula I in combination with: a bisphosphonate such as alendronate; estrogen, estrogens, and optionally progesterone; an estrogen agonist or antagonist; or calcitonin, and pharmaceutical compositions thereof are useful in treating **osteoporosis**. This invention also provides pharmaceutical compositions comprising a compound of formula I and GHRP-6, Hexarelin, GHRP-1, GRF, IGF-1, IFG-2 or B-HT920.

PA **Pfizer Inc.**, New York, NY, United States (U.S. corporation)

PRAI US 1995-9469P 19951228 (60) <--

AB . . . thereof, where the substituents are defined in the specification, which are growth hormone secretogogues useful for treatment and prevention of **osteoporosis**, congestive heart failure, frailty associated with aging, obesity; accelerating **bone fracture** repair, attenuating protein catabolic response after a major operation, reducing cachexia and protein loss due to chronic illness, accelerating wound. . . estrogen, estrogens, and optionally progesterone; an estrogen agonist or antagonist; or calcitonin, and pharmaceutical compositions thereof are useful in treating **osteoporosis**. This invention also provides pharmaceutical compositions comprising a compound of formula I and GHRP-6, Hexarelin, GHRP-1, GRF, IGF-1, IFG-2 or. . .

SUMM This invention relates to dipeptide compounds which are growth hormone secretagogues and are useful for the treatment and prevention of **osteoporosis**.

SUMM . . . the truncal region. Decreased skeletal and cardiac muscle mass and muscle strength lead to, a significant reduction in exercise capacity. **Bone** density is also reduced. Administration of exogenous growth hormone has been shown to reverse many of the metabolic changes. Additional. . .

SUMM The compounds of WO 94/11012 and WO 94/13696 are reported to be useful in the treatment of **osteoporosis** in combination with parathyroid hormone or a bisphosphonate.

SUMM a method for the treatment or prevention of **osteoporosis** which comprises administering to a human or other animal in need of such treatment or prevention an amount of a compound of Formula I which is effective in treating or preventing **osteoporosis**;

SUMM a method for the treatment or prevention of **osteoporosis** which comprises administering to a human or other animal with **osteoporosis** a combination of a bisphosphonate compound such as alendronate, and especially preferred is the bisphosphonate compound ibandronate, and a compound. . .

SUMM a method for the treatment -or prevention of **osteoporosis** which comprises administering to a human or other animal with **osteoporosis** a combination of estrogen or Premarin.RTM. and a compound of Formula I and optionally progesterone;

SUMM a method for the treatment of **osteoporosis** which comprises administering to a human or other animal with **osteoporosis** a combination of an estrogen agonist or antagonist such as tamoxifen, droloxifene, raloxifene and idoxifene and a compound of Formula. . .

SUMM a particularly preferred method for the treatment of **osteoporosis** comprises administering to a human or other animal with **osteoporosis** a combination of an estrogen agonist or antagonist such as Cis-6-(4fluoro-phenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5,6,7,8tetrahydro-naphthalene2-ol;

SUMM a method for the treatment of **osteoporosis** which comprises administering to a human or other animal with **osteoporosis** a combination of calcitonin and a compound of Formula I;

SUMM In another aspect, this invention provides methods for accelerating **bone fracture** repair, attenuating protein catabolic response after a major operation, reducing cachexia and protein loss due to chronic illness such as. . . effective in promoting release of endogenous growth hormone; of the instant method a preferred method of use is to accelerate **bone fracture** repair or for accelerating the recovery of patients having undergone major surgery.

SUMM . . . efficiency of animals raised for meat production to improve carcass quality; to increase milk production in dairy cattle; improvement of **bone** or wound healing and improvement in vital organ function. The compounds of the present invention by inducing endogenous GH secretion. . .

SUMM . . . Formula I or another compound which exhibits a different activity, e.g., an antibiotic growth permittant or an agent to treat **osteoporosis** or with other pharmaceutically active materials wherein the combination enhances efficacy and minimizes side effects.

SUMM . . . follows: stimulating growth hormone release in elderly humans; treating growth hormone deficient adults; preventing catabolic side effects of glucocorticoids, treating **osteoporosis**, stimulating the immune system, acceleration of wound healing, accelerating **bone fracture** repair, treating growth retardation, treating congestive heart failure as disclosed in PCT publications WO 95/128173 and WO 95/128174 (an example. . . as gastrointestinal surgery; treating intrauterine growth retardation, skeletal dysplasia, hypercortisonism and Cushings syndrome; replacing growth hormone in stressed patients; treating **osteochondrodysplasias**, Noonans syndrome, sleep disorders, Alzheimer's disease, delayed wound healing, and psychosocial deprivation; treating of pulmonary dysfunction and ventilator dependency; attenuating. . . improving muscle strength, increasing muscle mass, mobility, maintenance of skin thickness, metabolic homeostasis, renal hemeostasis in the frail elderly; stimulating **osteoblasts**, **bone** remodelling, and cartilage growth; treating neurological diseases such as peripheral and drug induced neuropathy, Guillian-Barre Syndrome, amyotrophic lateral sclerosis, multiple. . .

SUMM . . . one times the dose levels which are effective when these compounds and secretagogues are used singly. Combined therapy to inhibit **bone** resorption, prevent **osteoporosis**, reduce skeletal **fracture**, enhance the healing of **bone fractures**, stimulate **bone** formation and increase **bone** mineral density can be effectuated by combinations of bisphosphonates and the growth hormone secretagogues of this invention, see PCT publication. . . The use of bisphosphonates for these utilities has been reviewed, for example, by Hamdy, N.A.T., Role of Bisphosphonates in Metabolic **Bone** Diseases, Trends in Endocrinol. Metab., 1993, 4, pages 19-25. Bisphosphonates with these utilities include but are not limited to alendronate,. . . invention of between 0.01 mg/kg to 20 mg/kg of body weight are administered to patients to obtain effective treatment of **osteoporosis**.

SUMM . . . the second compound of this invention. The term estrogen agonist/antagonist refers to compounds which bind with the estrogen receptor, inhibit **bone** turnover and prevent **bone** loss. In particular, estrogen agonists are herein defined as chemical compounds capable of binding to the estrogen receptor sites in. . . activities are readily determined by those skilled in the art according to standard assays including estrogen receptor binding assays, standard **bone** histomorphometric and densitometer methods (see Eriksen E. F. et al., **Bone** Histomorphometry, Raven Press, New York, 1994, pages 1-74; Grier S. J. et al., The Use of Dual-Energy X-Ray Absorptiometry In Animals, Inv. Radiol., 1996, 31(1):50-62; Wahner H. W.

and Fogelman I., The Evaluation of **Osteoporosis**: Dual Energy X-Ray Absorptiometry in Clinical Practice., Martin Dunit Ltd., London 1994, pages 1-296). A variety of these compounds are. . .

SUMM The amount of the anti-resorptive agent to be used is determined by its activity as a **bone** loss inhibiting agent. This activity is determined by means of an individual compound's pharmacoidnetics and its minimal maximal effective dose in inhibition of **bone** loss using a protocol such as those referenced above.

SUMM In general an effective dosage for the activities of this invention, for example the treatment of **osteoporosis**, for the estrogen agonists/antagonists (when used in combination with a compound of Formula I of this invention) is in the. . .

CLM What is claimed is:

11. A method for treating or preventing **osteoporosis** which comprises administering to a human or other animal in need of such treatment or prevention an amount of a compound of claim 1 which is effective in treating or preventing **osteoporosis**.

14. A method for accelerating **bone fracture** repair, attenuating protein catabolic response after a major operation, reducing cachexia and protein loss due to chronic illness, accelerating wound. . .

16. A method for the treatment or prevention of **osteoporosis** which comprises administering to a human or other animal with **osteoporosis** a combination of a bisphosphonate compound and a compound of claim 1.

17. A method for the treatment of **osteoporosis** according to claim 16 wherein the bisphosphonate compound is alendronate.

18. A method for the treatment or prevention of **osteoporosis** which comprises administering to a human or other animal with **osteoporosis** a combination of estrogen or conjugated estrogens and a compound of claim 1 and optionally progesterone.

20. A method for the treatment of **osteoporosis** which comprises administering to a human or other animal with **osteoporosis** a combination of calcitonin and a compound of claim 1.

22. A method for the treatment of **osteoporosis** which comprises administering to a human or other animal with **osteoporosis** a combination of an estrogen agonist or antagonist and a compound of claim 1.

29. A method according to claim 14 wherein the method is for accelerating **bone fracture** repair.

31. A method for the treatment of **osteoporosis** according to claim 16 wherein the bisphosphonate compound is ibandronate.

IT Aging, animal
IT Obesity
IT **Osteoporosis**
(prepn. of nitrogen heterocyclic peptide analogs as growth-hormone secretagogues)

IT 193270-46-1P 193270-47-2P **193270-49-4P** 193270-50-7P
193270-51-8P 193270-52-9P 193270-53-0P 193270-54-1P 193270-55-2P
193270-56-3P 193270-57-4P 193270-58-5P 193270-59-6P 193270-60-9P
193270-61-0P 193270-62-1P 193270-63-2P 193270-64-3P 193270-68-7P
193270-70-1P 193270-71-2P 193270-72-3P 193270-73-4P 193270-76-7P
193270-78-9P 193270-81-4P 193270-86-9P 193270-90-5P 193270-94-9P
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193272-64-9P 193272-65-0P 193272-67-2P 193272-70-7P 193272-72-9P
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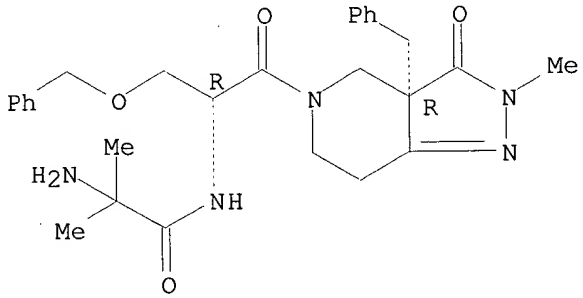
193273-79-9P 193273-80-2P 193273-81-3P 193273-82-4P 193273-83-5P
193273-84-6P 193273-85-7P 193273-86-8P 193273-87-9P 193273-88-0P
(prepn. of nitrogen heterocyclic peptide analogs as growth-hormone secretagogues)

IT **193270-49-4P 193273-65-3P 193273-66-4P**
193273-67-5P 193273-68-6P 193273-69-7P
(prepn. of nitrogen heterocyclic peptide analogs as growth-hormone secretagogues)

RN 193270-49-4 USPAT2

CN Propanamide, 2-amino-N-[(1R)-2-[(3aR)-2,3,3a,4,6,7-hexahydro-2-methyl-3-oxo-3a-(phenylmethyl)-5H-pyrazolo[4,3-c]pyridin-5-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl-, monohydrochloride (9CI) (CA INDEX NAME)

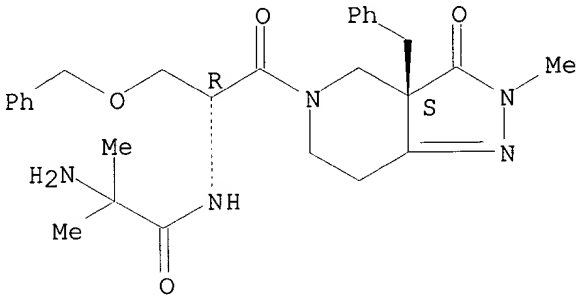
Absolute stereochemistry.



● HCl

RN 193273-65-3 USPAT2
CN Propanamide, 2-amino-N-[(1R)-2-[(3aS)-2,3,3a,4,6,7-hexahydro-2-methyl-3-oxo-3a-(phenylmethyl)-5H-pyrazolo[4,3-c]pyridin-5-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl-, monohydrochloride (9CI) (CA INDEX NAME)

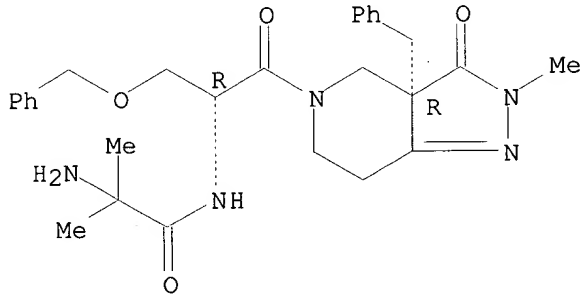
Absolute stereochemistry.



● HCl

RN 193273-66-4 USPAT2
CN Propanamide, 2-amino-N-[(1R)-2-[(3aR)-2,3,3a,4,6,7-hexahydro-2-methyl-3-oxo-3a-(phenylmethyl)-5H-pyrazolo[4,3-c]pyridin-5-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

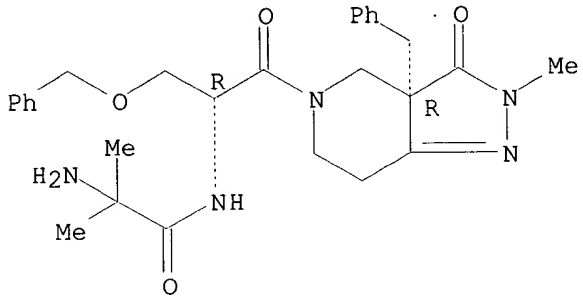


RN 193273-67-5 USPAT2
CN Propanamide, 2-amino-N-[(1R)-2-[(3aR)-2,3,3a,4,6,7-hexahydro-2-methyl-3-oxo-3a-(phenylmethyl)-5H-pyrazolo[4,3-c]pyridin-5-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl-, monomethanesulfonate (9CI) (CA INDEX NAME)

CM 1

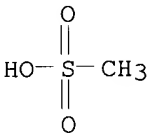
CRN 193273-66-4
CMF C28 H35 N5 O4

Absolute stereochemistry.



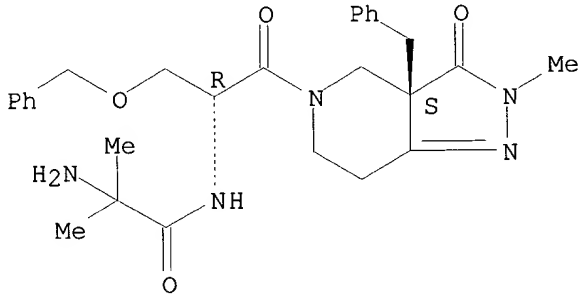
CM 2

CRN 75-75-2
CMF C H4 O3 S



RN 193273-68-6 USPAT2
CN Propanamide, 2-amino-N-[(1R)-2-[(3aS)-2,3,3a,4,6,7-hexahydro-2-methyl-3-oxo-3a-(phenylmethyl)-5H-pyrazolo[4,3-c]pyridin-5-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

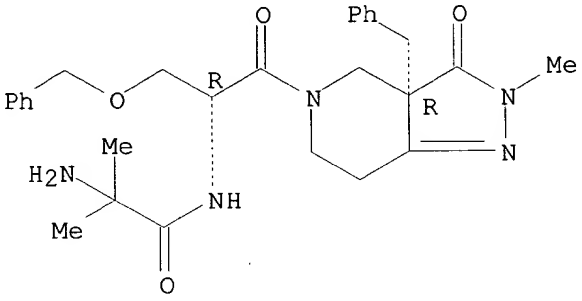


RN 193273-69-7 USPAT2
CN Propanamide, 2-amino-N-[(1R)-2-[(3aR)-2,3,3a,4,6,7-hexahydro-2-methyl-3-oxo-3a-(phenylmethyl)-5H-pyrazolo[4,3-c]pyridin-5-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl-, (2R,3R)-2,3-dihydroxybutanedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 193273-66-4
CMF C28 H35 N5 O4

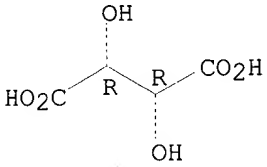
Absolute stereochemistry.



CM 2

CRN 87-69-4
CMF C4 H6 O6
CDES 1:R2:R*,R*

Absolute stereochemistry.



=> fil biosis
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FROM JANUARY 1969 TO DATE.

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L80 ANSWER 1 OF 1 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 1996:499731 BIOSIS
DN PREV199699222087
TI MK-0677, an oral GH secretagogue increases serum IGF-I in musculoskeletally impaired elderly subjects.
AU Bach, M. A. (1); Plotkin, D. (1); Bolognese, J. (1); Farmer, M. (1); Gelato, M.; Kaiser, F. E.; Kiel, D.; Korenman, S.; McKeever, C.; Munoz, D.; Schwartz, R.; Gormley, G. J.
CS (1) St. Petersburg, FL USA
SO Journal of the American Geriatrics Society, (1996) Vol. 44, No. 9, pp. S10.
Meeting Info.: 1996 Annual Meeting of the American Geriatrics Society and the American Federation for Aging Research
ISSN: 0002-8614.
DT Conference
LA English
CC General Biology - Symposia, Transactions and Proceedings of Conferences,

Congresses, Review Annuals 00520
Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Physiology, General and Miscellaneous - General 12002
Endocrine System - Pancreas *17008
Endocrine System - Pituitary *17014
Muscle - Pathology *17506
Bones, Joints, Fasciae, Connective and Adipose Tissue - Pathology *18006
Pharmacology - Endocrine System *22016
Gerontology *24500
BC Hominidae *86215
IT Major Concepts
Endocrine System (Chemical Coordination and Homeostasis); Geriatrics (Human Medicine, Medical Sciences); Muscular System (Movement and Support); Pharmacology; Skeletal System (Movement and Support)
IT Chemicals & Biochemicals
MK-0677; INSULIN-LIKE GROWTH FACTOR
IT Miscellaneous Descriptors
GERIATRICS; GROWTH HORMONE SECRETION; HORMONE-DRUG; INSULIN-LIKE GROWTH FACTOR; LEAN BODY MASS; MEETING ABSTRACT; MK-0677
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
human (Hominidae)
ORGN Organism Superterms
animals; chordates; humans; mammals; primates; vertebrates
RN **159634-47-6** (MK-0677)
61912-98-9 (INSULIN-LIKE GROWTH FACTOR)

=> fil wpix
FILE 'WPIX' ENTERED AT 07:18:44 ON 14 AUG 2003
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FILE LAST UPDATED: 13 AUG 2003 <20030813/UP>
MOST RECENT DERWENT UPDATE: 200352 <200352/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

>>> NEW WEEKLY SDI FREQUENCY AVAILABLE --> see NEWS <<<

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=> d all abeq tech abex tot l101

L101 ANSWER 1 OF 2 WPIX COPYRIGHT 2003 THOMSON DERWENT on STN
AN 2002-089896 [12] WPIX
DNC C2002-027743
TI Combination of growth hormone secretagogue and an antidepressant useful to

improve the physical or psychological condition of a patient e.g. cardiac function.

DC B05
IN BUSCH, F R; WELCH, W M
PA (BUSC-I) BUSCH F R; (WELC-I) WELCH W M; (PFIZ) PFIZER PROD INC
CYC 96
PI WO 2001089570 A2 20011129 (200212)* EN 66p A61K045-06
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
US 2002002137 A1 20020103 (200212) A61K038-05
AU 2001055013 A 20011203 (200221) A61K045-06
EP 1284753 A2 20030226 (200319) EN A61K045-06
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
BR 2001011002 A 20030415 (200334) A61K045-06
ADT WO 2001089570 A2 WO 2001-IB815 20010510; US 2002002137 A1 Provisional US 2000-207017P 20000525, US 2001-860786 20010518; AU 2001055013 A AU 2001-55013 20010510; EP 1284753 A2 EP 2001-928149 20010510, WO 2001-IB815 20010510; BR 2001011002 A BR 2001-11002 20010510, WO 2001-IB815 20010510
FDT AU 2001055013 A Based on WO 200189570; EP 1284753 A2 Based on WO 200189570; BR 2001011002 A Based on WO 200189570
PRAI US 2000-207017P 20000525; US 2001-860786 20010518
IC ICM A61K038-05; A61K045-06
ICS A61K031-4745; A61P003-00; A61P009-00; A61P021-00; A61P025-00
AB WO 200189570 A UPAB: 20020221
NOVELTY - A combination comprises a growth hormone secretagogue (GHS), and an antidepressant (I), their prodrugs or salts.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for a kit comprising:

(a) a first unit dosage form comprising GHS, its prodrug or salt and a carrier, vehicle or diluent;

(b) a second unit dosage form comprising an antidepressant, its prodrug or salt, and a carrier, vehicle or diluent; and

(c) a container.

ACTIVITY - Cardiant; Vulnerary; Neuroprotective; **Osteopathic**; Antidepressant.

MECHANISM OF ACTION - Norepinephrine reuptake blocker; Serotonin reuptake inhibitor; Monoamine oxidase inhibitor.

USE - To improve the physical or psychological condition of a patient (particularly cardiac function, metabolism, muscle tone or mental state); in surgical or dental procedure; in the treatment of musculoskeletal frailty in a mammal; in **bone** healing following facial reconstruction, maxillary reconstruction or mandibular reconstruction; in the treatment of congestive heart failure in a mammal; and for attenuating protein catabolic response after a major operation in a mammal (all claimed). The combination is also useful in the prevention, retardation and/or regression of **osteoporosis** and related **bone** disorders.

ADVANTAGE - The combination induces vertebral synostosis, enhances long **bone** extension, healing rate of **bone** graft or prosthetic ingrowth, and increases muscle mass. The combination increases **bone** density, reduces fat mass and total serum cholesterol. The combination results in improved cardiac output, wound healing and higher metabolism.

Dwg.0/0

FS CPI
FA AB; GI; DCN
MC CPI: B04-C01A; B04-C01B; B06-H; B07-H; B10-A18; B10-B02F; B10-B03B; B10-B04B; B14-D05A; B14-F01; B14-J01; B14-J01A1; B14-J04; B14-J05;

B14-L06; **B14-N01**; B14-N06

TECH UPTX: 20020221

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Compounds: (GHS) is of formula (I), its stereoisomeric mixture, diastereomerically enriched, diastereomerically pure, enantiomerically enriched or enantiomerically pure isomer.

Het = heterocyclic moiety of formula (i)-(v) (preferably (iii));

d, n, w = 0-2 (preferably n is 0 and w is 2, n is 1 and w is 1, or n is 2 and w is 0);

e = 1 or 2;

f = 0 or 1 (preferably 0);

Y2 = oxygen or sulfur;

A = -NR2-C(O)-NR2-, -NR2-S(O)2-NR2-, -O-C(O)-NR2-, -NR2-C(O)-O-, -C(O)-NR2-C(O)-, -C(O)-NR2-C(R9R10)-, -C(R9R10)-NR2-C(O)-, -C(R9R10)-C(R9R10)-C(R9R10)-, -S(O)2-C(R9R10)-C(R9R10)-, -C(R9R10)-O-C(O)-, -C(R9R10)-O-C(R9R10)-, -NR2-C(O)-C(R9R10)-, -O-C(O)-C(R9R10)-, -C(R9R10)-C(O)-NR2-, -C(O)-NR2-C(O)-, -C(R9R10)-C(O)-O-, -C(O)-NR2-C(R9R10)-C(R9R10)-, -C(O)-O-C(R9R10)-, -C(R9R10)-C(R9R10)-C(R9R10)-C(R9R10)-, -S(O)2-NR2-C(R9R10)-C(R9R10)-, -C(R9R10)-C(R9R10)-NR2-C(O)-, -C(R9R10)-C(R9R10)-O-C(O)-, -NR2-C(O)-C(R9R10)-C(R9R10)-, -NR2-S(O)2-C(R9R10)-C(R9R10)-, -O-C(O)-C(R9R10)-C(R9R10)-, -C(R9R10)-C(R9R10)-C(O)-NR2-, -C(R9R10)-C(R9R10)-C(O)-, -C(R9R10)-NR2-C(O)-O-, -C(R9R10)-O-C(O)-NR2-, -C(R9R10)-NR2-C(O)-NR2-, -NR2-C(O)-O-C(R9R10)-, -NR2-C(O)-NR2-C(R9R10)-, -NR2-S(O)2-NR2-C(R9R10)-, -O-C(O)-NR2-C(R9R10)-, -C(O)-N=C(R11)-NR2-, -C(O)-NR2-C(R11)=N-, -C(R9R10)-NR12-C(R9R10)-, -NR12-C(R9R10)-, -NR12-C(R9R10)-C(R9R10)-, -C(O)-O-C(R9R10)-C(R9R10)-, -NR2-C(R11)=N-C(O)-, -C(R9R10)-C(R9R10)-N(R12)-, -C(R9R10)-NR12-, -N=C(R11)-NR2-C(O)-, -C(R9R10)-C(R9R10)-NR2-S(O)2-, -C(R9R10)-C(R9R10)-S(O)2-NR2-, -C(R9R10)-C(R9R10)-C(O)-O-, -C(R9R10)-S(O)2-C(R9R10)-, -C(R9R10)-C(R9R10)-S(O)2-, -C(O)-C(R9R10)-C(R9R10)- or -C(R9R10)-NR2-S(O)2-NR2- (where the left hand side of the radical is connected to C and the right hand side is connected to C');

Q = covalent bond or CH2;

W = CH or N;

X = CR9R10, C=CH2 or C=O;

Y = CR9R10, O or NR2;

Z = C=O, C=S or S(O)2;

G1 = H, halo, hydroxy, nitro, amino, cyano, phenyl, carboxyl, -CONH2, -(1-4C) alkylthio, phenoxy, -COO(1-4C)alkyl, N,N-di-(1-4C)alkylamino, -(3-6C)cycloalkyl (optionally substituted by at least one 1-4C alkyl, halogen or hydroxy), -(1-4C) alkylamino carbonyl, di-(1-4C)alkylamino carbonyl or T;

T = -(1-4C)alkyl, -(1-4C)alkoxy, -(2-6C)alkenyl or -(2-6C)alkynyl (all optionally substituted by at least one phenyl, halogen or hydroxy);

G2, G3 = H, halo, hydroxy or T';

T' = -(1-4C)alkyl or -(1-4C) alkoxy (both optionally mono-, di- or tri-substituted by halo);

R1 = H, -CN, -TN(X6)C(O)X6, -TN(X6)C(O)T''-A1, -TN(X6)S(O)2T''-A1, -TN(X6)S(O)2X6, -TN(X6)C(O)N(X6)T''-A1, -TN(X6)C(O)N(X6)(X6), -TC(O)N(X6)(X6), -TC(O)N(X6)T''-A1, -TC(O)OX6, -TC(O)TO''-A1, -TOX6, -TOC(O)X6, -TOC(O)T''-A1, -TOC(O)N(X6)T''-A1, -TOC(O)N(X6)(X6), -TC(O)X6, -TC(O)T'-A1, -TN(X6)C(O)OX6, -TN(X6)S(O)2N(X6)(X6), -TS(O)mX6, -TS(O)mT''-A1, -(1-10C)alkyl, -T''-A1, -T-(3-7C)cycloalkyl, -T-Y1-(1-6C)alkyl, -T-Y1-T'-A1 or -T-Y1-T''-(3-7C)cycloalkyl (where the (cyclo)alkyl groups are optionally substituted by 1-4C alkyl or T1);

T = (CH2)q (optionally substituted by T1 or 1-2 (1-4C) alkyl);

T'' = (CH2)t (optionally substituted by T1);

T1 = hydroxy, 1-4C alkoxy, carboxyl, -CONH2, -S(O)m(1-6C)alkyl, -CO2(1-4C)alkyl ester, 1H-tetrazoyl-5-yl or 1-3 fluoro groups;

Y1 = O, S(O)m, -C(O)NX6-, -CH=CH-, -C triple bond C-, -N(X6)C(O)-, -C(O)NX6-, -C(O)O-, -OC(O)N(X6)- or -OC(O)-;

q = 0-4;

t = 0-3;
R1a = H, F, Cl, Br, I, 1-6C alkyl, phenyl(1-3C)alkyl, pyridyl(1-3C)alkyl, thiazolyl(1-3C)alkyl or thienyl(1-3C)alkyl;
R2 = H, 1-8C alkyl, -(0-3C)alkyl-(3-8C)cycloalkyl, -(1-4C)alkyl-A1 or A1 (where the (cyclo)alkyl groups are optionally substituted by hydroxy, -C(O)OX6, -C(O)N(X6)(X6), -N(X6)(X6), -S(O)m(1-6C)alkyl, -C(O)A1, -C(O)(X6), CF3, CN or 1-3 halo groups);
R3 = A1, 1-10C alkyl, -(1-6C)alkyl-A1, -(1-6C)alkyl-(3-7C)cycloalkyl, -(1-5C)alkyl-X1-(1-5C)alkyl, -(1-5C)alkyl-X1-(0-5C)alkyl-A1 or -(1-5C)alkyl-X1-(1-5C)alkyl-(3-7C)cycloalkyl (where the alkyl group is optionally substituted by -S(O)m(1-6C)alkyl, -C(O)OX3, 1-5 halo or 1-3 -OX3);
X1 = O, S(O)m, -N(X2)C(O)-, -C(O)N(X2)-, -OC(O)-, -C(O)O-, -CX2=CX2-, -N(X2)C(O)O-, -OC(O)N(X2)- or - C triple bond C-;
R4 = H, 1-6C alkyl or 3-7C cycloalkyl;
CR3R4 = (5-7C)cycloalkyl, (5-7C)cycloalkenyl, partially saturated or fully saturated 4-8 membered ring containing 1-4 O, S or N, or a bicyclic ring containing a partially or fully saturated 5-6 membered ring, fused to a partially or fully saturated 5-6 membered ring (optionally containing 1-4 N, S or O);
X4 = H or 1-6C alkyl;
NX4R4C- = 5-6 membered ring;
R6 = bond or -Z1-(CH2)a-C(X5)(X5a)-(CH2)b-;
X5, X5a = H, CF3, A1, 1-6C alkyl (optionally substituted by A1, OX2, -S(O)m(1-6C) alkyl, -C(O)OX2, (3-7C)cycloalkyl, -N(X2)(X2) or -C(O)N(X2)(X2)) or the carbon containing X5 or X5a forms 1 or 2 1-5C alkylene with the nitrogen atom containing R7 and R8;
X5+X5a = partially or fully saturated 3-7 membered ring, 4-8 membered ring (containing 1-4 N, S or O) or a bicyclic ring (consisting of a partially or fully saturated 5-6 membered ring (optionally containing 1 or 2 N, S or O), fused to a 5-6 membered ring (optionally containing 1-4 N, S or O));
Z1 = bond, O or N-X2;
R6 = -(CRaRb)a-E-(CRaRb)b-;
E = -O-, -S-, -CH=CH- or E1;
E1 = xylenyl, pyridinyl, pyrimidinyl, naphthalenyl, thiophenyl, 1H-imidazolyl or thiazolyl (all optionally mono-, di- or tri-substituted by halo, hydroxy, -N(Rc)(Rc), (1-6C)alkyl or (1-6C)alkoxy);
Ra, Rb = H, (1-6C)alkyl, trifluoromethyl, phenyl or 1-6C alkyl (monosubstituted by imidazolyl, naphthyl, phenyl, indolyl, para-hydroxyphenyl, -ORc, S(O)mRc, C(O)ORc, (3-7C)cycloalkyl, -N(Rc)(Rc), -C(O)N(Rc)(Rc));
Ra+R7, Ra+E, Rb+R7 or Rb+E = 1-8C alkylene bridge between the terminal nitrogen and the alkyl portion of Ra or Rb and the R7 or E (where E is other than O, S or -CH=CH-);
Ra+Rb = (3-7C)cycloalkyl;
Rc = H or 1-6C alkyl;
a, b = 0-3;
R7, R8 = H or (1-6C alkyl (optionally substituted by A1, -C(O)O-(1-6C)alkyl, -S(O)m(1-6C)alkyl, 1-5 halo groups, 1-3 hydroxy, 1-3 -O-C(O)(1-10C)alkyl or 1-3 (1-6C)alkoxy);
R7+R8 = -(CH2)r-L-(CH2)r-;
L = C(X2)(X2), S(O)m or N(X2);
R9, R10 = H, fluoro, hydroxy or (1-5C)alkyl (optionally mono-, di-, tri-, tetra- or penta-substituted by halo);
R11 = 1-5C alkyl or phenyl (optionally mono-, di- or tri-substituted by 1-5C alkyl, halo or 1-5C alkoxy);
R12 = (1-5C) -alkylsulfonyl, -alkanoyl or -alkyl (the alkyl portion of all is optionally mono-, di-, tri-, tetra- or penta-substituted by halo);
A1 = (5-7C cycloalkenyl, phenyl, 4-8 membered ring (optionally containing 1-4 O, S or N) or a bicyclic ring (consisting of a 5-6 membered ring (optionally containing 1-4 N, O or S) fused to a 5 - 6 membered ring (optionally containing 1-4 O, S or N)) (all optionally mono-, di- or tri-substituted by F, Cl, Br, I, OCF3, OCF2H, CF3, CH3, OCH3, -OX6,

-C(O)N(X6)(X6), -C(O)OX6, oxo. (1-6C alkyl, nitro, cyano, benzyl, -S(O)m(1-6C)alkyl, 1H-tetrazol-5-yl, phenyl, phenoxy, phenylalkyloxy, halophenyl, methylenedioxy, -N(X6)(X6), -N(X6)C(O)(X6), -SO2N(X6)(X6), -N(X6)S(O)2-phenyl, -N(X6)S(O)2X6, -CONX11X12, -S(O)2NX11X12, -NX6S(O)2X12, -NX6CONX11X12, -NX6S(O)2NX11X12, -NX6C(O)X12, imidazolyl, thiazolyl or tetrazolyl);
X11 = H or (1-6C)alkyl (optionally substituted by phenyl, phenoxy, (1-6C)alkoxycarbonyl, -S(O)m(1-6C)alkyl, 1-5 halo, 1-3 hydroxy, 1-3 (1-10C)alkanoyloxy or 1-3 (1-6C)alkoxy);
X12 = H, 1-6C alkyl, phenyl, thiazolyl, imidazolyl, furyl or thienyl (all optionally mono-, di- or tri-substituted by Cl, F, CH3, OCH3, OCF3 or CF3);
X11+X12 = -(CH2)r-L1-(CH2)r-;
L1 = L or O;
r = 1-3;
X2 = H, 1-6C alkyl or (3-7C)cycloalkyl (both optionally substituted by -S(O)m(1-6C)alkyl, -C(O)OX3, 1 - 5 halo or 1 - 3 OX3);
X3 = H or 1-6C alkyl;
X6 = H, (2-6C)halogenated alkyl, (3-7C) halogenated cycloalkyl or X'6;
X'6 = 1-6C alkyl or 3-7C cycloalkyl (both optionally mono- or di-substituted by (1-4C)alkyl, hydroxy, (1-4C)alkoxy, carboxyl, CONH2, -S(O)m(1-6C)alkyl, carboxylate, (1-4C)alkyl ester or 1H-tetrazol-5-yl);
X7 = H or (1-6C)alkyl (optionally substituted by hydroxy); and
m = 0-2;
provided that both n and w cannot be 0 simultaneously, R1a is other than F, Cl, Br or I, when a heteroatom is vicinal to C. When 1 alkylene bridge is formed then only one of X5 or X5a is on the carbon atoms and only one of R7 or R8 is on the nitrogen atom. When 2 alkylene bridges are formed then X5 and X5a cannot be on the carbon atoms, and R7 and R8 cannot be on the nitrogen atom. When a and b are both 0, then Z1 is other than N-X2 or O. If E is -O- or -S-, b is other than 0 or 1, and if E is -CH=CH-, then b is other than 0. A1 is optionally substituted by only one methylenedioxy. When there are 2 X6 (both 1-6C alkyl) on one atom, then the 2 X6 groups are optionally joined to form 4 - 9 membered ring (optionally containing O, S or NX7). X6 and X12 are other than H when attached to C(O) or S(O)2. When R6 is a bond then L is N(X2) and each r is 2 or 3.
TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Compounds: (I) Is a norepinephrine reuptake inhibitor (NERI), selective serotonin reuptake inhibitor (SSRI), monoamine oxidase inhibitor (MAO), combined NERI/SSRI, an atypical antidepressant, their prodrugs or salts (preferably SSRI).

ABEX UPTX: 20020221

SPECIFIC COMPOUNDS - 2-Amino-N-(1(R)-benzyloxymethyl-2-(1,3-dioxo-8a(S)-pyridin-2-ylmethyl-2-(2,2,2-trifluoroethyl)-hexahydro-imidazo(1,5-a)pyrazin-7-yl)-2-oxo-ethyl)-2-methyl-propionamide, 2-amino-N-(2-(3a-(R)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo-(4,3-c)pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl)-isobutyramide, 2-amino-N-(1-(R)-(2,4-difluoro-benzyloxymethyl)-2-oxo-2-(3-oxo-3a-(R)-pyridin-2-ylmethyl)-2-(2,2,2-trifluoroethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo(4,3-c)pyridin-5-yl)-ethyl)-2-methyl propionamide, their L-(+)-tartaric acid salt, hexarelin, ipamorelin, **MK-0677**, NN703, L-162752, L-163022, GPA-748, KP102, GHRP-2 and LY444711 are specifically claimed as GHS. Citalopram, femoxetine, fluoxatine, fluvoxamine, indalpine, indeloxazine, milnacipran, paroxetine, sertraline, sibutramine, zimeldine, their prodrugs or salts are specifically claimed as SSRI.

ADMINISTRATION - The combination is administered orally, parenterally, intraduodenally, intramuscularly, transcutaneously, subcutaneously, intramedullary or transdermally. No dosage given.

EXAMPLE - No suitable example given.

L101 ANSWER 2 OF 2 WPIX COPYRIGHT 2003 THOMSON DERWENT on STN
AN 1997-457195 [42] WPIX

DNC C1997-145894
TI New composition for treatment of **osteoporosis** - comprising an oestrogen agonist or antagonist and a prostaglandin or prostaglandin agonist or antagonist..
DC B02 B03
IN KE, H Z; THOMPSON, D D; THOMPSON, D
PA (PFIZ) PFIZER INC; (PFIZ) PFIZER CORP; (KEHZ-I) KE H Z; (THOM-I) THOMPSON D D
CYC 50
PI WO 9731640 A1 19970904 (199742)* EN 79p A61K031-557
RW: AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL OA PT SE
W: AU BG BR BY CA CN CZ HU IL IS JP KR KZ LK LV MX NO NZ PL RO RU SG SI SK TR UA US UZ VN
AU 9710398 A 19970916 (199803) A61K031-557
ZA 9701719 A 19981028 (199848) 75p A61K000-00
NO 9803936 A 19980827 (199849) A61K031-557
EP 883404 A1 19981216 (199903) EN A61K031-557
R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU LV NL PT RO SE SI
AU 703285 B 19990325 (199924) A61K031-557
JP 11504352 W 19990420 (199926) 91p A61K045-00
CN 1209064 A 19990224 (199927) A61K031-557
CZ 9802718 A3 19990616 (199929) A61K031-557
BR 9612533 A 19990720 (199940) A61K031-557
HU 9904123 A2 20000528 (200035) A61K031-557
SK 9801183 A3 20000711 (200050) A61K031-5575
MX 9807004 A1 19990101 (200051) A61K031-557
KR 99087337 A 19991227 (200059) A61K031-557
NZ 323456 A 20010330 (200121) A61K033-16
US 2001009920 A1 20010726 (200146) A61K031-20
US 6323232 B1 20011127 (200175) A61K031-40
TW 464496 A 20011121 (200248) A61K031-435
EP 1236475 A2 20020904 (200266) EN A61K045-06
R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU LV NL PT RO SE SI
RU 2190395 C2 20021010 (200279) A61K031-135
JP 2002308771 A 20021023 (200302) 32p A61K031-4535
ADT WO 9731640 A1 WO 1996-IB1462 19961223; AU 9710398 A AU 1997-10398 19961223; ZA 9701719 A ZA 1997-1719 19970227; NO 9803936 A WO 1996-IB1462 19961223, NO 1998-3936 19980827; EP 883404 A1 EP 1996-941153 19961223, WO 1996-IB1462 19961223; AU 703285 B AU 1997-10398 19961223; JP 11504352 W WO 1996-IB1462 19961223, JP 1997-530738 19961223; CN 1209064 A CN 1996-180058 19961223; CZ 9802718 A3 WO 1996-IB1462 19961223, CZ 1998-2718 19961223; BR 9612533 A BR 1996-12533 19961223, WO 1996-IB1462 19961223; HU 9904123 A2 WO 1996-IB1462 19961223, HU 1999-4123 19961223; SK 9801183 A3 WO 1996-IB1462 19961223, SK 1998-1183 19961223; MX 9807004 A1 MX 1998-7004 19980827; KR 99087337 A WO 1996-IB1462 19961223, KR 1998-706746 19980827; NZ 323456 A NZ 1996-323456 19961223, WO 1996-IB1462 19961223; US 2001009920 A1 Provisional US 1996-12412P 19960228, Div ex WO 1996-IB1462 19961223, Div ex US 1998-117972 19980811, US 2000-736051 20001213; US 6323232 B1 Provisional US 1996-12412P 19960228, WO 1996-IB1462 19961223, US 1998-117972 19980811; TW 464496 A TW 1996-115770 19961220; EP 1236475 A2 Div ex EP 1996-941153 19961223, EP 2002-10920 19961223; RU 2190395 C2 WO 1996-IB1462 19961223, RU 1998-117620 19961223; JP 2002308771 A Div ex JP 1997-530738 19961223, JP 2002-54756 19961223
FDT AU 9710398 A Based on WO 9731640; EP 883404 A1 Based on WO 9731640; AU 703285 B Previous Publ. AU 9710398, Based on WO 9731640; JP 11504352 W Based on WO 9731640; CZ 9802718 A3 Based on WO 9731640; BR 9612533 A Based on WO 9731640; HU 9904123 A2 Based on WO 9731640; KR 99087337 A Based on WO 9731640; NZ 323456 A Based on WO 9731640; US 6323232 B1 Based on WO 9731640; EP 1236475 A2 Div ex EP 883404; RU 2190395 C2 Based on WO 9731640
PRAI US 1996-12412P 19960228; US 1998-117972 19980811; US 2000-736051 20001213
REP 2.Jnl.Ref; EP 509317; EP 635270; US 4894373; US 5281590; WO 9621656
IC ICM A61K000-00; A61K031-135; A61K031-20; A61K031-40; A61K031-435;

A61K031-4535; A61K031-557; A61K031-5575; A61K033-16; A61K045-00; A61K045-06

ICS A01N037-00; A61K031-13; A61K031-138; A61K031-38; A61K031-381; A61K031-41; A61K031-437; A61K031-44; A61K031-4418; A61K031-4439; A61K031-445; A61K031-4453; A61K031-4462; A61K031-4725; A61K031-495; A61K038-00; A61K038-22; A61K038-27; A61K038-29; **A61P019-08**; **A61P019-10**; A61P043-00; C07C000-00; C07D000-00; C07G000-00

ICI A61K031-557, A61K031:135, A61K031:38; A61K031:135, A61K031:38, A61K033-16; A61K031:135, A61K031:38, A61K038-29; A61K031:135, A61K031:38, A61K038-27; A61K031-445, A61K031:135, A61K031:38; A61K031-4535, A61K031:4439; A61K031-557, A61K031:135; A61K031-557, A61K031:135, A61K031:38; A61K031:135, A61K031:38, A61K033-16; A61K031:135, A61K031:38, A61K038-29; A61K031:135, A61K031:38, A61K038-27; A61K031-445, A61K031:135, A61K031:38

AB WO 9731640 A UPAB: 19971021

A first new pharmaceutical composition comprises: (a) a therapeutically effective amount of an oestrogen agonist/antagonist; and (b) a therapeutically effective amount of a prostaglandin or a prostaglandin agonist/antagonist. Also claimed are: (1) A second composition comprising (a) a therapeutically effective amount of droloxifene, raloxifene, tamoxifen or idoxifene; and (b) a therapeutically effective amount of sodium fluoride or N-(1(R)-(1,2- dihydro-1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1'- yl)carbonyl)-2-(phenylmethylethyloxy)ethyl-2-amino-2-methylpropanamide:**MK-677**. (2) A third composition comprising (a) a therapeutically effective amount of cis-6-(4-fluoro-phenyl)-5-(4-(2-piperidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydro-naphthalene-2-ol; (-)-cis-6-phenyl-5-(4-(2-pyrrolidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydro-naphthalene-2-ol; cis-6-phenyl-5-(4-(2-pyrrolidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydro-naphthalene-2-ol; cis-1-(6'-pyrrolidinoethoxy-3 '-pyri dyl)-2-phenyl-6-hydroxy-1,2,3,4-tetrahydronaphthalene; 1-(4'-pyrrolidinoethoxyphenyl)-2-(4''-fluorophenyl)-6-hydroxy-1,2,3,4-tetrahydroisoquinoline; cis-6-(4-hydroxyphenyl)-5-(4-(2-piperidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydronaphthalene-2-ol or 1-(4'-pyrrolidinoethoxyphenyl)-2-phenyl-6-hydroxy-1,2,3,4-tetrahydroisoquinoline; and (b) a therapeutically effective amount of sodium fluoride, a parathyroid hormone, growth hormone or a growth hormone secretagogue. (3) a fourth composition comprising (a) a therapeutically effective amount of raloxifene, tamoxifen or idoxifene; and (b) a therapeutically effective amount of a parathyroid hormone, growth hormone or a growth hormone secretagogue. (4) A composition containing (a) a first compound being droloxifene, raloxifene, tamoxifen or idoxifene and (b) a second compound being sodium fluoride or **MK-677**, where the amount of first compound alone and the amount of second compound alone is insufficient to achieve the therapeutic effects of increase in **bone** formation and decrease in **bone resorption** if administered simultaneously (sic) and where the combined effects of the first and second compounds is greater than the sum of the therapeutic effects achievable with the individual amounts of the two compounds. (5) Kits containing each composition as a treatment for low **bone** mass comprising therapeutically effective amounts of the first and second compounds in unit dosage form and a container for the dosage forms.

USE - The compositions are useful for treating low **bone** mass in mammals, particularly in **osteoporosis**. The first and second compounds are administered simultaneously or the second compound is administered for about three months to three years followed by the first compound for at least three months.

ADVANTAGE - The combined effect of the amounts of the first and second compounds is greater than the sum of the therapeutic effects achievable with the individual amounts of the first and second compounds.

Dwg.0/0

FS CPI

FA AB; DCN

MC CPI: B06-D03; B07-D02; B07-D05; B14-D02; B14-D02A; B14-L04; B14-L08; **B14-N01**

=> d his

(FILE 'HOME' ENTERED AT 06:25:04 ON 14 AUG 2003)
SET COST OFF

FILE 'HCAPLUS' ENTERED AT 06:26:07 ON 14 AUG 2003
L1 1 S US20010009920/PN
SEL RN

FILE 'REGISTRY' ENTERED AT 06:26:39 ON 14 AUG 2003
L2 24 S E1-E24
L3 2 S L2 AND 4/NR
L4 1 S L3 NOT I/ELS
L5 1 S 159634-47-6
L6 6 S C27H36N4O5S/MF AND (46.150.18 AND 2189.10.1)/RID
L7 3 S L6 NOT (14C# OR 35S)
L8 4 S L4,L7
L9 15 S L2 AND 46.150.18/RID
L10 13 S L9 NOT L3,L8

FILE 'HCAPLUS' ENTERED AT 06:34:43 ON 14 AUG 2003
E KE H/AU
L11 31 S E3,E5
L12 39 S E28,E31,E32,E35
E THOMPSON D/AU
L13 197 S E3,E12
L14 51 S E88,E91
L15 81 S E102,E103
L16 366 S L11-L15
L17 365 S L16 NOT L1

FILE 'REGISTRY' ENTERED AT 06:36:03 ON 14 AUG 2003

FILE 'HCAPLUS' ENTERED AT 06:36:04 ON 14 AUG 2003
SET SMARTSELECT ON
L18 SEL L17 1- RN : 1629 TERMS
SET SMARTSELECT OFF

FILE 'REGISTRY' ENTERED AT 06:36:16 ON 14 AUG 2003
L19 1629 S L18
L20 15 S L19 AND 46.150.18/RID AND N2C3-NC5/ES AND 4/NR
L21 2 S L20 AND C28H35N5O4
L22 1 S 193273-66-4
L23 4 S C28H35N5O4/MF AND (46.150.18 AND 333.165.22)/RID AND 4/NR
L24 3 S L23 NOT 14C
L25 6 S L7,L24
SEL RN
L26 10 S E1-E6/CRN
L27 9 S L26 NOT CONJUGATE
L28 15 S L8,L25,L27

FILE 'REGISTRY' ENTERED AT 06:40:37 ON 14 AUG 2003

FILE 'HCAOLD' ENTERED AT 06:42:13 ON 14 AUG 2003
L29 0 S L28

FILE 'HCAPLUS' ENTERED AT 06:42:26 ON 14 AUG 2003
L30 109 S L28
L31 51 S L163191 OR L()(163191 OR 163 191) OR IBUTAMOREN? IR IBUTAMORE

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L32          126 S L30,L31
L33           20 S L32 AND (PD<=19960228 OR PRD<=19960228 OR AD<=19960228)
L34            1 S L16 AND L33
L35            2 S PFIZER?/PA,CS AND L33
L36            2 S L34,L35
                 E OSTEOPOROSIS/CT
L37         8694 S E3-E7
                 E E3+ALL
L38         8695 S E6+NT
                 E E5+ALL
                 E BONE/CT
L39         1022 S E15
L40         2173 S E33
L41         5431 S E56,E57
L42         2108 S E116
L43         3282 S E164
L44         6360 S E188
L45          362 S E200
L46          158 S E207
L47         8361 S E230,E231
                 E E3+ALL
L48        57681 S E8,E9
L49          362 S E12
L50        82713 S E8+NT
L51         4583 S E40+NT OR E41+NT OR E42+NT
L52         4856 S E36+NT OR E37+NT
                 E E38+ALL
L53         9467 S E4,E5,E3
L54        64316 S E3+NT
                 E BONE/CT
                 E E79+ALL
L55         1022 S E2
                 E BONE DEMINERALIZATION/CT
                 E E60+ALL
L56          921 S E2
                 E BONE REMINERALIZATION/CT
                 E BONE DENSITY/CT
                 E BONE RESORPTION/CT
                 E E4+ALL
                 E BONE(L)RESORPTION/CT
L57         5431 S BONE/CT(L)RESORPTION
L58            3 S L33 AND L37-L57
L59            3 S L33 AND (?OSTEO? OR BONE OR ?OSSO?)
L60            3 S L36,L58,L59
L61           17 S L33 NOT L60
L62            1 S L33 AND FRACTUR?
L63            3 S L60,L62

     FILE 'HCAPLUS' ENTERED AT 06:54:13 ON 14 AUG 2003

     FILE 'USPATFULL, USPAT2' ENTERED AT 06:54:28 ON 14 AUG 2003
L64           65 S L32
L65           20 S L64 AND (PFIZER?/PA OR THOMPSON D?/AU OR KE H?/AU)
L66           11 S L64 AND (PD<=19960228 OR PRD<=19960228)
L67            7 S L65 AND L66
L68            8 S L66 AND (OSTEO? OR OSSO? OR BONE? OR RESORPT?)/CT
L69           10 S L66 AND (?OSTEO? OR BONE OR ?OSSO? OR FRACTUR?)
L70            2 S L69 NOT L68
L71           10 S L68-L70
L72            7 S L67 AND L71
L73           10 S L71,L72
L74            1 S L66 NOT L73
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     FILE 'BIOSIS' ENTERED AT 06:59:03 ON 14 AUG 2003
L75           72 S L32
L76           12 S L75 AND PY<=1996
L77            1 S L76 AND (?OSTEO? OR BONE OR ?OSSO? OR FRACTUR?)
L78            1 S L76 AND 1800?/CC
L79            2 S L77,L78
L80            1 S L79 AND BONE?/CC
L81            3 S L75 AND (THOMPSON D? OR KE H?)/AU
L82            0 S L76 AND L81

     FILE 'BIOSIS' ENTERED AT 07:02:09 ON 14 AUG 2003

     FILE 'EMBASE' ENTERED AT 07:02:31 ON 14 AUG 2003
L83          117 S L32
                 E 2 AMINO N 2 BENZYLOXY 1 1 2 DIHYDRO 1 METHANESULFONYLSPIRO 3H
                 E "2 AMINO N [2 BENZYLOXY 1 [1,2 DIHYDRO 1 METHANESULFONYLSPIRO
                 E 2 AMINO N 2 BENZYLOXY 1/CT
                 E 2 AMINO N 2 (BENZYLOXY 1/CT
                 E 2 AMIN N/CT
                 E 2 AMINO N/CT
                 E "2 AMINO N (BENZYLOXY"/CT
                 E "2 AMINO N BENZYLOXY"/CT
                 E "2 AMINO N (2 BENZYLOXY"/CT
                 E "2 AMINO N (2 BENZYLOXY 1 (1 2 DIHYDRO 1 METHANESULFONYLSPIRO
L84            6 S E4-E14
L85           76 S MK0677 OR MK 0677
L86          139 S L83-L85
L87           12 S L86 AND PY<=1996
L88            2 S L87 AND (?OSTEO? OR BONE? OR ?OSSO? OR FRACTUR? OR DEMINERAL
                 E OSTEOPOROSIS/CT
                 E E3+ALL
L89            0 S L87 AND E11+NT
                 E BONE FRACTURE/CT
                 E E3+ALL
L90            0 S L87 AND E2+NT
L91            0 S L87 AND (E4+NT OR E6+NT)
L92            0 S E8+NT AND L87
L93            0 S E9+NT AND L87
                 E BONE DENSITY/CT
L94            0 S L87 AND E3+NT
                 E BONE DEMINERALIZATION/CT
L95            0 S L87 AND E3+NT

     FILE 'WPIX' ENTERED AT 07:12:23 ON 14 AUG 2003
L96            3 S L31/BIX OR L85/BIX
L97            1 S L96 AND A61P019/IC,ICM,ICS,ICA,ICI
L98            2 S L96 AND (B14-N01 OR C14-N01 OR B12-J08 OR C12-J08)/MC
L99            2 S L97,L98
L100           2 S L96 AND (?OESTEO? OR ?OSTEO? OR BONE OR FRACTUR? OR ?OSSO? O
L101           2 S L99,L100

     FILE 'WPIX' ENTERED AT 07:18:44 ON 14 AUG 2003
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=> fil hcaplus
FILE 'HCAPLUS' ENTERED AT 07:26:51 ON 14 AUG 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2003 AMERICAN CHEMICAL SOCIETY (ACS)
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FILE COVERS 1907 - 14 Aug 2003  VOL 139 ISS 7
FILE LAST UPDATED: 13 Aug 2003  (20030813/ED)

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.


=> d all hitstr tot 16

L6   ANSWER 1 OF 22  HCAPLUS  COPYRIGHT 2003 ACS on STN
AN   1997:633307  HCAPLUS
DN   127:234319
TI   Preparation of aminoalkanoyl spiropiperidides and analogs as growth
     hormone-release stimulators
IN   Smith, Roy G.; Gormley, Glenn J.; Polvino, William J.
PA   Merck and Co., Inc., USA
SO   Brit. UK Pat. Appl., 107 pp.
     CODEN: BAXXDU
DT   Patent
LA   English
IC   ICM  A61K031-445
CC   28-2 (Heterocyclic Compounds (More Than One Hetero Atom))
     Section cross-reference(s): 1, 2
FAN.CNT 1
     PATENT NO.        KIND  DATE           APPLICATION NO.  DATE
     ---------------   ----  --------       ---------------  --------
PI   GB 2308064         A1   19970618       GB 1996-22440    19961029 <--
PRAI US 1995-8133             19951031  <--
     GB 1996-9696             19960509
OS   MARPAT 127:234319
GI
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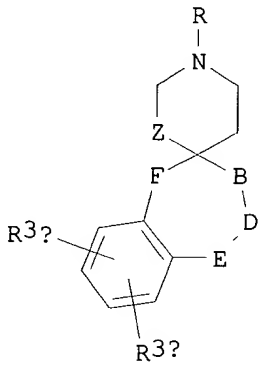
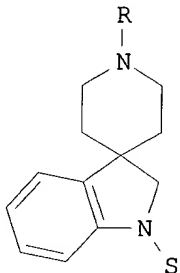
Jan Delaval
Reference Librarian
Biotechnology & Chemical Library
(703) 308-4307 – 703-308-4498
jan.delaval@uspto.gov



I



II

AB Title compds. [e.g., I; B, D, E, F = bond, CR8R10, O, CO, SO0-2, NR9; 1 of BD or DE may = N:CR10 or CR10:N and the other of B, E, F = O, SO0-2, NR9; R = COCR1R2NR6COZ1NR4R5; R1 = (alkoxy)alkyl, aryl(alkyl), etc.; R2 = H, (cyclo)alkyl, etc.; R3a,R3b = H, halo, alkyl, alkoxy, etc.; R4,R5 = H, alkyl, etc.; NR4R5 = heterocyclyl; R6 = H or alkyl; R8,R10 = H, groups cited for R2, OR2, aryl(alkyl), etc.; R9 = groups cited for R2, aryl(alkyl), COR2, etc.; Z = CH2 or CH2CH2; Z1 = (un)substituted (imino- or oxy-) alkylene] were prepd. as growth hormone-release stimulators (no data). Thus, 1'-methyl-1,2-dihydrospiro[3H-indole-3,4'-piperidine] was N-sulfonated and the demethylated product amidated by (R)-PhCH2OCH2CH(NHCO2CMe3)CO2H to give title compd. II [R = (R)-COCH(NHR7)CH2OCH2Ph](III; R7 = CO2CMe3) which was deprotected and the product amidated by HO2CCMe2NHCO2CMe3 to give, after deprotection, III (R7 = COCMe2NH2).

ST spiropiperidide aminoalkanoyl prepn growth hormone stimulator

IT Heart, disease
(failure, treatment; prepn. of aminoalkanoyl spiropiperidides and analogs as growth hormone-release stimulators)

IT 145455-80-7P **159633-92-8P** 159633-99-5P 159634-42-1P
159634-43-2P 159634-44-3P 159634-46-5P **159634-47-6P**
159634-49-8P 159634-50-1P 159634-51-2P 159634-52-3P 159634-53-4P
159634-54-5P 159634-55-6P 159634-56-7P 159634-57-8P 159634-58-9P
159752-10-0P 165125-48-4P 170842-84-9P 195248-01-2P
195248-02-3P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of aminoalkanoyl spiropiperidides and analogs as growth hormone-release stimulators)

IT 9002-72-6, Growth hormone
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(prepn. of aminoalkanoyl spiropiperidides and analogs as growth hormone-release stimulators)

IT 114343-29-2P
RL: BYP (Byproduct); PREP (Preparation)
(prepn. of aminoalkanoyl spiropiperidides and analogs as growth hormone-release stimulators)

IT 76-83-5, Trityl chloride 100-39-0, Benzyl bromide 100-47-0, Benzonitrile, reactions 100-51-6, Benzyl alcohol, reactions 107-18-6, 2-Propen-1-ol, reactions 529-34-0, 1-Tetralone 597-43-3, 2,2-Dimethylbutanedioic acid 624-31-7, 4-Iodotoluene 873-75-6, 4-Bromobenzyl alcohol 5006-62-2, Ethyl nipecotate 5241-64-5, N-tert-Butoxycarbonyl-D-tryptophan 5465-63-4, 2-Bromobenzylamine hydrochloride 15030-72-5, N-Benzyloxycarbonyl-2-methylalanine 24424-99-5, Di-tert-butyl dicarbonate 30992-29-1, N-tert-Butoxycarbonyl-

2-methylalanine 47173-80-8 58479-61-1, tert-Butyldiphenylsilyl chloride 69584-91-4 81445-45-6, (R)-2-Benzyloxypropanal 82732-07-8 86499-24-3
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of aminoalkanoyl spiropiperidides and analogs as growth hormone-release stimulators)

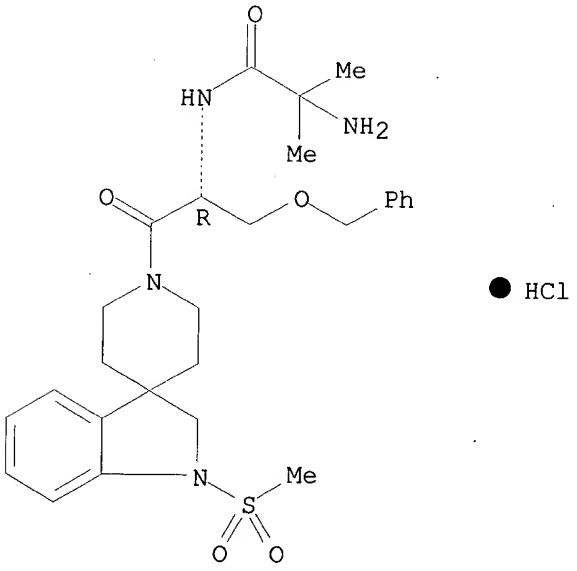
IT 3349-64-2P, 1-Tetralone oxime 4424-80-0P, 2,3,4,5-Tetrahydro-1H-1-benzazepine-2-one 18039-42-4P, 5-Phenyltetrazole 51219-55-7P 54043-71-9P, 2,2-Dimethylbutanedioic acid, 4-methyl ester 86499-35-6P 87268-78-8P, 5-Phenyl-2-trityltetrazole 128182-82-1P 130250-54-3P 133051-88-4P 133776-42-8P 133909-97-4P 137036-54-5P 137036-55-6P 140700-64-7P 141595-98-4P 145457-70-1P 145486-45-9P 148289-82-1P 159634-86-3P 159634-87-4P 159634-88-5P 159634-89-6P 159634-93-2P 159634-94-3P 159634-96-5P 162356-90-3P 162356-92-5P 162356-93-6P 165125-50-8P 165125-51-9P 168059-24-3P 170842-80-5P 170842-81-6P 170842-83-8P 180465-66-1P 180465-67-2P 195248-03-4P 195248-04-5P 195248-05-6P 195248-06-7P 195248-07-8P 195248-08-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of aminoalkanoyl spiropiperidides and analogs as growth hormone-release stimulators)

IT 170842-82-7P
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of aminoalkanoyl spiropiperidides and analogs as growth hormone-release stimulators)

IT **159633-92-8P 159634-47-6P 159752-10-0P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of aminoalkanoyl spiropiperidides and analogs as growth hormone-release stimulators)

RN 159633-92-8 HCAPLUS
CN Propanamide, 2-amino-N-[(1R)-2-[1,2-dihydro-1-(methylsulfonyl)spiro[3H-indole-3,4'-piperidin]-1'-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl-, monohydrochloride (9CI) (CA INDEX NAME)

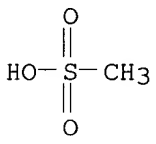
Absolute stereochemistry.



● HCl

RN 159634-47-6 HCAPLUS
CN Propanamide, 2-amino-N-[(1R)-2-[1,2-dihydro-1-(methylsulfonyl)spiro[3H-indole-3,4'-piperidin]-1'-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-

CRN 75-75-2
CMF C H4 O3 S



L6 ANSWER 2 OF 22 HCAPLUS COPYRIGHT 2003 ACS on STN
AN 1997:557139 HCAPLUS
Correction of: 1997:416107
DN 127:156806
Correction of: 127:76095
TI Modulation of pulsatile GH release through a novel receptor in hypothalamus and pituitary gland
AU Smith, Roy G.; Pong, Sheng-Shung; Hickey, Gerry; Jacks, Tom; Cheng, Kang; Leonard, Reid; Cohen, Charles J.; Arena, Joseph P.; Chang, Ching H.; Drisko, Jennifer; Wyvratt, Matt; Fisher, Mike; Nargund, Ravi; Patchett, Art
CS Dep. Biochem., Merck Res. Lab., Rahway, NJ, 07065, USA
SO Recent Progress in Hormone Research (**1996**), Volume Date 1995, 51, 261-286
CODEN: RPHRA6; ISSN: 0079-9963
PB Endocrine Society
DT Journal; General Review
LA English
CC 2-0 (Mammalian Hormones)
AB A review, with 59 refs. Hormone replacement should provide a serum hormone profile similar to that found in normal physiol. This is generally impractical because hormones are usually released episodically and therefore require frequent administration. However, rather than replacing the hormone directly, in theory, one could administer a mimic or amplifier of the pulse generator that controls pulsatile release of the particular hormone. Using growth hormone (GH) as a paradigm the authors sought such a mimetic that would provide episodic GH release when administered by the oral route. A GH secretagogue, **MK0677**, is described that has these ideal properties; following oral administration **MK0677** amplifies episodic GH release. Mechanistically, it synergizes with growth hormone releasing hormone (GHRH) through a receptor and signal transduction pathway distinct from that of GHRH and is a functional antagonist of somatostatin (SRIF). **MK0677** also acts on the arcuate nucleus and appears to stimulate GHRH release. By using 35S-**MK0677**, a new G-protein coupled receptor for **MK0677** was characterized in the plasma membrane fraction of pituitary and hypothalamic tissue. The receptor is present in very low abundance and couples to phospholipase C. Other ligands selective for this receptor also cause synchronization of well-defined pathways leading to GH release. Reported oral treatment of dogs once daily with **MK0677** initiates amplified pulsatile GH release accompanied by increases in IGF-1 that sustained. The unique biol. properties of **MK0677** and other synthetic ligands that bind to the same receptor force the authors to predict that these ligands mimic a naturally occurring hormone that regulates pulsatile GH release. Understanding the regulatory mechanisms involved in this paradigm has broad implications for the control of pulsatile rhythms in the endocrine system.
ST review **MK0677** somatotropin secretion receptor
IT Pituitary gland
(**MK0677** modulation of pulsatile growth hormone release through novel receptor in hypothalamus and pituitary gland)

IT Receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**MK0677** modulation of pulsatile growth hormone release through novel receptor in hypothalamus and pituitary gland)

IT Brain
(hypothalamus; **MK0677** modulation of pulsatile growth hormone release through novel receptor in hypothalamus and pituitary gland)

IT **159752-10-0, MK 677**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**MK0677** modulation of pulsatile growth hormone release through novel receptor in hypothalamus and pituitary gland)

IT 9002-72-6, Growth hormone
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**MK0677** modulation of pulsatile growth hormone release through novel receptor in hypothalamus and pituitary gland)

IT **159752-10-0, MK 677**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**MK0677** modulation of pulsatile growth hormone release through novel receptor in hypothalamus and pituitary gland)

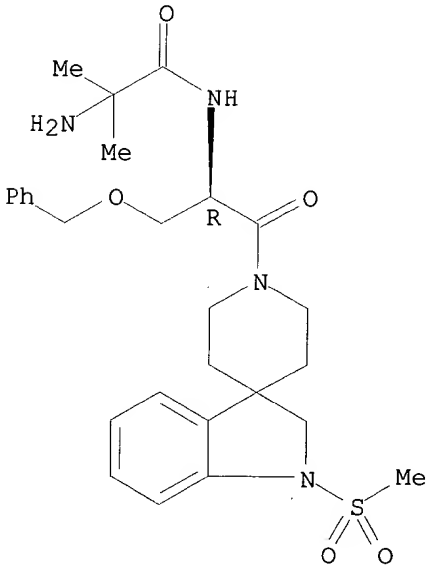
RN 159752-10-0 HCAPLUS

CN Propanamide, 2-amino-N-[(1R)-2-[1,2-dihydro-1-(methylsulfonyl)spiro[3H-indole-3,4'-piperidin]-1'-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl-, monomethanesulfonate (9CI) (CA INDEX NAME)

CM 1

CRN 159634-47-6
CMF C27 H36 N4 O5 S

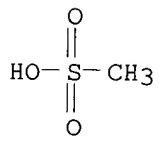
Absolute stereochemistry.



CM 2

CRN 75-75-2

CMF C H4 O3 S



L6 ANSWER 3 OF 22 HCAPLUS COPYRIGHT 2003 ACS on STN
AN 1997:416107 HCAPLUS
DN 127:76095
TI Modulation of pulsatile GH release through a novel receptor in hypothalamus and pituitary gland
AU Wyvratt, Matt; Fisher, Mike; Nargund, Ravi; Patchett, Art; Cheng, Kang; Leonard, Reid; Cohen, Charles J.; Arena, Joseph P.; Chang, Ching H.; Drisko, Jennifer
CS Merck Research Laboratories, Departments of Biochemistry and Physiology, Rahway, NJ, 07065, USA
SO Recent Progress in Hormone Research (**1996**), Volume Date 1995, 51, 261-286
CODEN: RPHRA6; ISSN: 0079-9963
PB Endocrine Society
DT Journal; General Review
LA English
CC 2-0 (Mammalian Hormones)
AB A review, with 59 refs. Hormone replacement should provide a serum hormone profile similar to that found in normal physiol. This is generally impractical because hormones are usually released episodically and therefore require frequent administration. However, rather than replacing the hormone directly, in theory, one could administer a mimic or amplifier of the pulse generator that controls pulsatile release of the particular hormone. Using growth hormone (GH) as a paradigm the authors sought such a mimetic that would provide episodic GH release when administered by the oral route. A GH secretagogue, **MK0677**, is described that has these ideal properties; following oral administration **MK0677** amplifies episodic GH release. Mechanistically, it synergizes with growth hormone releasing hormone (GHRH) through a receptor and signal transduction pathway distinct from that of GHRH and is a functional antagonist of somatostatin (SRIF). **MK0677** also acts on the arcuate nucleus and appears to stimulate GHRH release. By using 35S-**MK0677**, a new G-protein coupled receptor for **MK0677** was characterized in the plasma membrane fraction of pituitary and hypothalamic tissue. The receptor is present in very low abundance and couples to phospholipase C. Other ligands selective for this receptor also cause synchronization of well-defined pathways leading to GH release. Reported oral treatment of dogs once daily with **MK0677** initiates amplified pulsatile GH release accompanied by increases in IGF-1 that are sustained. The unique biol. properties of **MK0677** and other synthetic ligands that bind to the same receptor force the authors to predict that these ligands mimic a naturally occurring hormone that regulates pulsatile GH release. Understanding the regulatory mechanisms involved in this paradigm has broad implications for the control of pulsatile rhythms in the endocrine system.
ST review **MK0677** pulsatile GH receptor
IT Pituitary gland
(**MK0677** modulation of pulsatile GH release through novel receptor in hypothalamus and pituitary gland)
IT Growth hormone receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(**MK0677** modulation of pulsatile GH release through novel receptor in hypothalamus and pituitary gland)

IT Brain
(hypothalamus; **MK0677** modulation of pulsatile GH release through novel receptor in hypothalamus and pituitary gland)

IT **159752-10-0, MK 677**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**MK0677** modulation of pulsatile GH release through novel receptor in hypothalamus and pituitary gland)

IT 9002-72-6, Growth hormone
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**MK0677** modulation of pulsatile GH release through novel receptor in hypothalamus and pituitary gland)

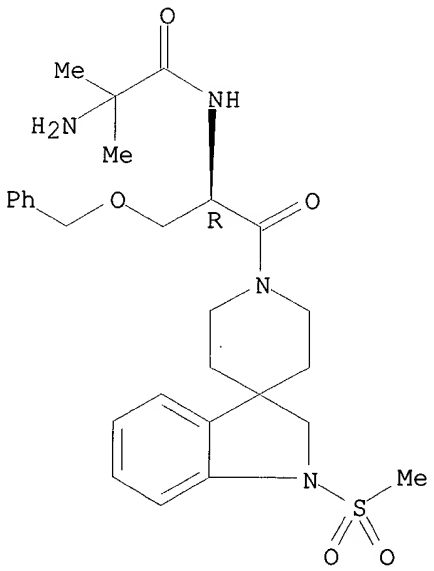
IT **159752-10-0, MK 677**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**MK0677** modulation of pulsatile GH release through novel receptor in hypothalamus and pituitary gland)

RN 159752-10-0 HCAPLUS
CN Propanamide, 2-amino-N-[(1R)-2-[1,2-dihydro-1-(methylsulfonyl)spiro[3H-indole-3,4'-piperidin]-1'-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl-, monomethanesulfonate (9CI) (CA INDEX NAME)

CM 1

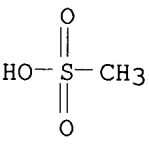
CRN 159634-47-6
CMF C27 H36 N4 O5 S

Absolute stereochemistry.



CM 2

CRN 75-75-2
CMF C H4 O3 S



L6 ANSWER 4 OF 22 HCAPLUS COPYRIGHT 2003 ACS on STN
AN 1997:394288 HCAPLUS
DN 127:5081
TI Preparation of polymorphic forms of a growth hormone release stimulant
IN Draper, Jerome P.; Dubost, David C.; Kaufman, Michael J.; Mccauley, James A.; Vandrilla, Jennifer L.; Varsolona, Richard J.
PA Merck and Co., Inc., USA; Draper, Jerome P.; Dubost, David C.; Kaufman, Michael J.; Mccauley, James A.; Vandrilla, Jennifer L.; Varsolona, Richard J.
SO PCT Int. Appl., 85 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C07D471-10
ICS A61K031-445
CC 28-2 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1, 63
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9715574	A1	19970501	WO 1996-US16955	19961023 <--
	W: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, HU, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	AU 9674686	A1	19970515	AU 1996-74686	19961023 <--
	AU 707946	B2	19990722		
	JP 10512295	T2	19981124	JP 1996-516737	19961023 <--
	BR 9611229	A	19990525	BR 1996-11229	19961023 <--
	EP 1019402	A1	20000719	EP 1996-936869	19961023 <--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
	JP 3204266	B2	20010904	JP 1997-516737	19961023 <--
	ZA 9608989	A	19970429	ZA 1996-8989	19961025 <--
	NO 9801867	A	19980629	NO 1998-1867	19980424 <--
	HK 1017894	A1	20010928	HK 1999-102961	19990712 <--
PRAI	US 1995-5900P	P	19951027 <--		
	GB 1996-3361	A	19960216 <--		
	WO 1996-US16955	W	19961023		

AB The title stimulant (no data), N-[1(R)-[(1,2-dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(phenylmethoxy)ethyl]-2-amino-2-methylpropanamide methanesulfonate was prepd. in a multistep synthesis and converted to multiple characterized polymorphic forms. The instant polymorphic forms have advantages over the other known forms in terms of thermodn. stability and suitability for inclusion in pharmaceutical formulations.
ST growth hormone release stimulant prepn polymorphic
IT Polymorphism (crystal)
(prepn. of polymorphic forms of a growth hormone release stimulant)
IT **159633-92-8P 159634-47-6P 159752-10-0P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(prepn. of polymorphic forms of a growth hormone release stimulant)

IT 100-63-0, Phenylhydrazine 498-94-2, Isonipecotic acid 501-53-1, Benzyl chloroformate 30992-29-1 47173-80-8, N-tert-Butoxycarbonyl-O-benzyl-D-serine 69584-91-4
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of polymorphic forms of a growth hormone release stimulant)

IT 10314-98-4P 138163-08-3P 159634-86-3P 159634-87-4P 167484-18-6P 178261-41-1P 180465-66-1P 180465-67-2P 184289-84-7P 184289-85-8P 190250-07-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of polymorphic forms of a growth hormone release stimulant)

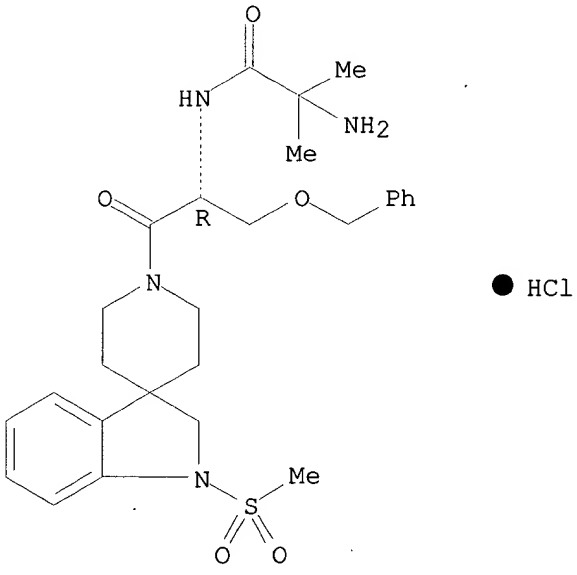
IT 184289-83-6P
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of polymorphic forms of a growth hormone release stimulant)

IT 9002-72-6, Growth hormone
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(release; stimulants; prepn. of polymorphic forms of a growth hormone release stimulant)

IT **159633-92-8P 159634-47-6P 159752-10-0P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of polymorphic forms of a growth hormone release stimulant)

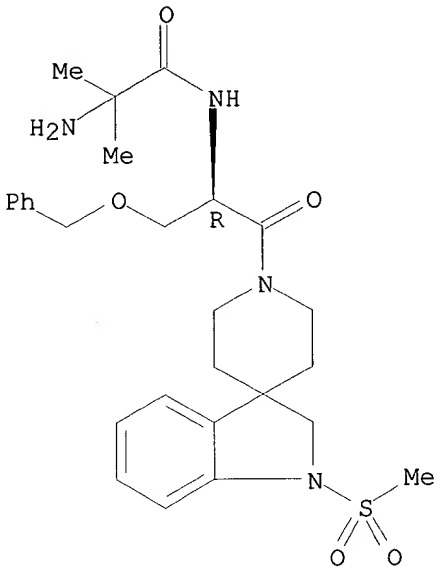
RN 159633-92-8 HCAPLUS
CN Propanamide, 2-amino-N-[(1R)-2-[1,2-dihydro-1-(methylsulfonyl)spiro[3H-indole-3,4'-piperidin]-1'-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 159634-47-6 HCAPLUS
CN Propanamide, 2-amino-N-[(1R)-2-[1,2-dihydro-1-(methylsulfonyl)spiro[3H-indole-3,4'-piperidin]-1'-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

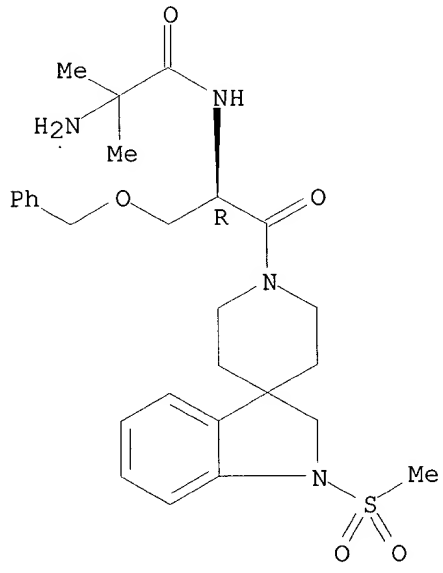


RN 159752-10-0 HCAPLUS
CN Propanamide, 2-amino-N-[(1R)-2-[1,2-dihydro-1-(methylsulfonyl)spiro[3H-indole-3,4'-piperidin]-1'-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl-, monomethanesulfonate (9CI) (CA INDEX NAME)

CM 1

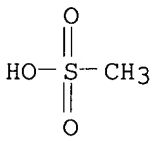
CRN 159634-47-6
CMF C27 H36 N4 O5 S

Absolute stereochemistry.



CM 2

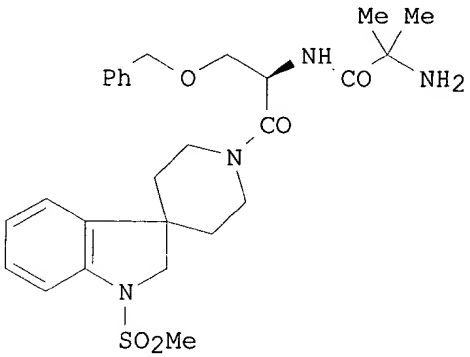
CRN 75-75-2
CMF C H4 O3 S



L6 ANSWER 5 OF 22 HCAPLUS COPYRIGHT 2003 ACS on STN
AN 1997:389204 HCAPLUS
DN 127:5009
TI Process for the preparation of a growth hormone secretagogue
IN Houghton, Peter G.; Houpis, Ioannis; Molina, Audrey; Lynch, Joseph E.; Volante, Ralph P.
PA Merck and Co., Inc., USA; Houghton, Peter G.; Houpis, Ioannis; Molina, Audrey; Lynch, Joseph E.; Volante, Ralph P.
SO PCT Int. Appl., 77 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C07D471-10
ICS A61K031-445
CC 27-11 (Heterocyclic Compounds (One Hetero Atom))
Section cross-reference(s): 2, 34
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9715573	A1	19970501	WO 1996-US16954	19961023 <--
	W: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, HU, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	AU 9674685	A1	19970515	AU 1996-74685	19961023 <--
	EP 863900	A1	19980916	EP 1996-936868	19961023 <--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, SI, FI, RO				
	CN 1204334	A	19990106	CN 1996-199084	19961023 <--
	BR 9610887	A	19990713	BR 1996-10887	19961023 <--
	JP 11513984	T2	19991130	JP 1996-516736	19961023 <--
	US 6028196	A	20000222	US 1998-51847	19980422 <--
PRAI	US 1995-5898P	P	19951027 <--		
	GB 1996-2949	A	19960213 <--		
	WO 1996-US16954	W	19961023		

OS CASREACT 127:5009; MARPAT 127:5009
GI



I

AB Propanamide I, which has the ability to stimulate the release of natural or endogenous growth hormone (no data), was prepd. starting from isonipecotic acid, phenylhydrazine, N-(tert-butoxycarbonyl)-O-benzyl-D-serine, and N-(tert-butoxycarbonyl)-.alpha.-methylalanine.

ST growth hormone secretalogue prepn; spiroindolepiperidine prepn growth hormone secretalogue

IT 9002-72-6, Somatotropin
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(deficiency; prepn. of a growth hormone secretagogue)

IT 9002-72-6, Growth hormone
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(prepn. of a growth hormone secretagogue)

IT 10314-98-4P 10314-99-5P 138163-08-3P **159634-47-6P**
159634-87-4P 167484-18-6P 178261-41-1P 180465-66-1P 180465-67-2P
184289-84-7P 184289-85-8P 190250-07-8P
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of a growth hormone secretagogue)

IT 159634-86-3P **159752-10-0P**
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(prepn. of a growth hormone secretagogue)

IT 56-23-5, Carbon tetrachloride, uses 67-66-3, Chloroform, uses 71-43-2, Benzene, uses 75-05-8, Acetonitrile, uses 75-09-2, uses 95-50-1, 1,2-Dichlorobenzene 107-06-2, 1,2-Dichloroethane, uses 107-12-0, Propionitrile 108-21-4, Isopropyl acetate 108-88-3, Toluene, uses 108-90-7, uses 141-78-6, Ethyl acetate, uses
RL: NUU (Other use, unclassified); USES (Uses)
(prepn. of a growth hormone secretagogue)

IT 75-64-9, tert-Butyl amine, reactions 75-75-2, Methanesulfonic acid 100-63-0, Phenylhydrazine 498-94-2, Isonipecotic acid 501-53-1, Benzyl chloroformate 538-75-0, DCC 2592-95-2 30992-29-1 47173-80-8
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of a growth hormone secretagogue)

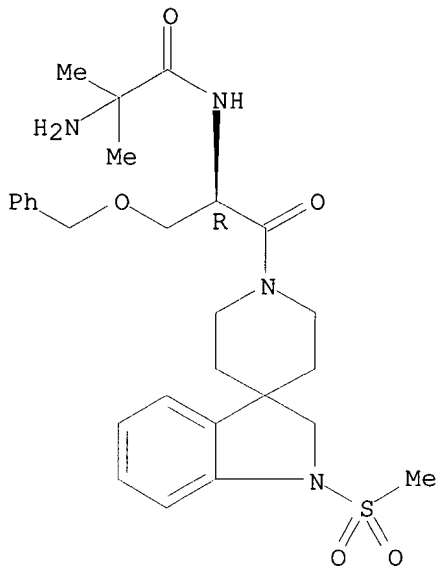
IT 184289-83-6P
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of a growth hormone secretagogue)

IT **159634-47-6P**
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of a growth hormone secretagogue)

RN 159634-47-6 HCAPLUS

CN Propanamide, 2-amino-N-[(1R)-2-[1,2-dihydro-1-(methylsulfonyl)spiro[3H-indole-3,4'-piperidin]-1'-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

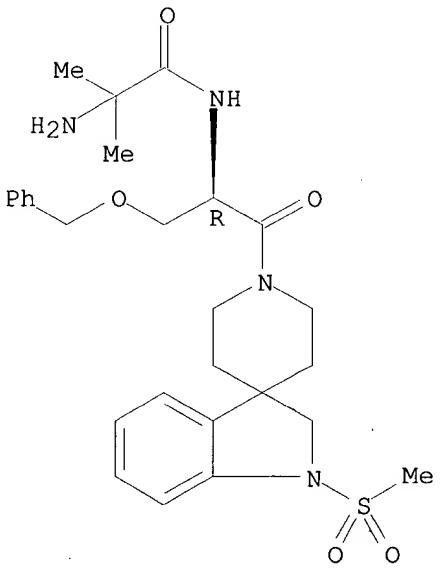


IT **159752-10-0P**
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(prepn. of a growth hormone secretagogue)
RN 159752-10-0 HCAPLUS
CN Propanamide, 2-amino-N-[(1R)-2-[1,2-dihydro-1-(methylsulfonyl)spiro[3H-indole-3,4'-piperidin]-1'-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl-, monomethanesulfonate (9CI) (CA INDEX NAME)

CM 1

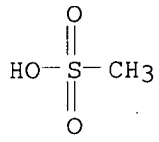
CRN 159634-47-6
CMF C27 H36 N4 O5 S

Absolute stereochemistry.



CM 2

CRN 75-75-2
CMF C H4 O3 S



L6 ANSWER 6 OF 22 HCAPLUS COPYRIGHT 2003 ACS on STN
AN 1997:377877 HCAPLUS
DN 126:347314
TI Wet granulation formulation of a growth hormone secretagogue
IN Asgharnejad, Mandana; Draper, Jerome P.; Dubost, David C.; Kaufman, Michael J.; Storey, David E.
PA Merck and Co., Inc., USA; Asgharnejad, Mandana; Draper, Jerome P.; Dubost, David C.; Kaufman, Michael J.; Storey, David, E.
SO PCT Int. Appl., 90 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A01N043-38
ICS A01N043-42; A61K031-40; A61K031-445
CC 63-6 (Pharmaceuticals)
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9715191	A1	19970501	WO 1996-US17196	19961023 <--
	W: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, HU, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	CA 2234817	AA	19970501	CA 1996-2234817	19961023 <--
	AU 9675228	A1	19970515	AU 1996-75228	19961023 <--
	EP 857020	A1	19980812	EP 1996-937761	19961023 <--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
	JP 11513989	T2	19991130	JP 1996-516841	19961023 <--
	US 6123964	A	20000926	US 1998-66469	19981027 <--
PRAI	US 1995-5897P	P	19951027 <--		
	US 1995-5901P	P	19951027 <--		
	GB 1996-3238	A	19960216 <--		
	GB 1996-3834	A	19960223 <--		
	WO 1996-US17196	W	19961023		

AB The present invention relates to a pharmaceutical compn. and a process for the prepn. of a tablet contg. a growth hormone secretagogue as the active ingredient. The tablet is prepd. by forming a powder blend of the active ingredient N-[1(R)-[(1,2-dihydro-1-methanesulfonyl-spiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyl-oxy)ethyl]-2-amino-2-methyl-propanamide, or a pharmaceutically acceptable salt thereof, in particular the methanesulfonate salt, with a binder/diluent, a first diluent, a second diluent, a first portion of a disintegrant, and a lubricant; wet granulating the powder blend with a soln. of ethanol/water to form granules; drying the granules to remove the ethanol/water; adding a second portion of a disintegrant; lubricating the granules; and compressing the

dried granules into the desired tablet form. The present invention further relates to a novel amorphous form of the compd. N-[1(R)-[(1,2-dihydro-1-methanesulfonyl-spiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(phenylmethyl-oxy)ethyl]-2-amino-2-methylpropanamide methanesulfonate which is produced directly as a result of the process of tablet formulation.

ST growth hormone secretagogue tablet wet milling

IT Drug delivery systems
(tablets; formulation of tablets of growth hormone secretagogues using a wet granulation step)

IT Granulation
(wet; formulation of tablets of growth hormone secretagogues using a wet granulation step)

IT 9003-39-8, Polyvinylpyrrolidone 9004-64-2, Hydroxypropyl cellulose 9004-65-3, Hydroxypropylmethylcellulose
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(binder or diluent; formulation of tablets of growth hormone secretagogues using a wet granulation step)

IT 37486-48-9P
RL: BYP (Byproduct); SPN (Synthetic preparation); PREP (Preparation)
(byproduct in prepn. growth hormone secretagogue; formulation of tablets of growth hormone secretagogues using a wet granulation step)

IT 63-42-3, Lactose 7757-93-9, Dibasic calcium phosphate
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(diluent; formulation of tablets of growth hormone secretagogues using a wet granulation step)

IT 74811-65-7, Croscarmellose sodium
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(disintegrant; formulation of tablets of growth hormone secretagogues using a wet granulation step)

IT **159634-47-6D**, salts **159752-10-0**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(formulation of tablets of growth hormone secretagogues using a wet granulation step)

IT 57-11-4, Stearic acid, biological studies 557-04-0, Magnesium stearate 1592-23-0, Calcium stearate
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(lubricant; formulation of tablets of growth hormone secretagogues using a wet granulation step)

IT 9004-34-6, Cellulose, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(microcryst., diluent; formulation of tablets of growth hormone secretagogues using a wet granulation step)

IT 9005-25-8, Starch, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pregelatinized, binder or diluent; formulation of tablets of growth hormone secretagogues using a wet granulation step)

IT **159634-47-6**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prepn. and formulation of; formulation of tablets of growth hormone secretagogues using a wet granulation step)

IT 10314-98-4P 10314-99-5P 138163-08-3P 159634-86-3P 159634-88-5P 165125-51-9P 167484-18-6P 178261-41-1P 180465-66-1P 180465-67-2P 184289-83-6P 184289-84-7P 184289-85-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and reactions in prepn. growth hormone secretagogue; formulation of tablets of growth hormone secretagogues using a wet granulation step)

IT **159633-92-8** 159634-87-4
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prepn. and reactions in prepn. growth hormone secretagogue; formulation of tablets of growth hormone secretagogues using a wet

granulation step)

IT 159634-89-6P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and reactions of, in prepn. growth hormone secretagogue; formulation of tablets of growth hormone secretagogues using a wet granulation step)

IT 121-44-8, Triethylamine, reactions 124-63-0, Methanesulfonyl chloride 23680-31-1 30992-29-1 69584-91-4 190005-79-9
RL: RCT (Reactant); RACT (Reactant or reagent)
(reactions of, in prepn. growth hormone secretagogue; formulation of tablets of growth hormone secretagogues using a wet granulation step)

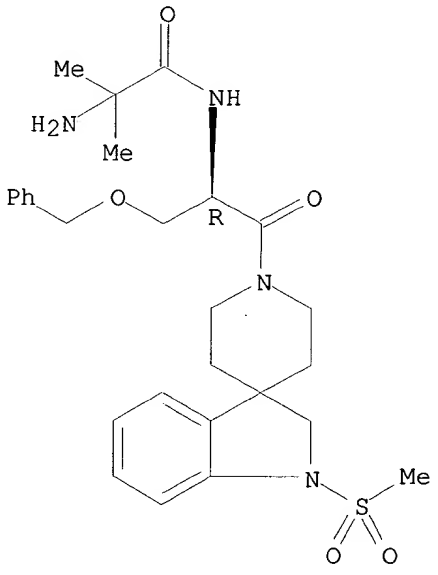
IT 498-94-2P, Isonipecotic acid
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(reactions of, in prepn. growth hormone secretagogue; formulation of tablets of growth hormone secretagogues using a wet granulation step)

IT 9002-72-6, Growth hormone
RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(secretagogues for; formulation of tablets of growth hormone secretagogues using a wet granulation step)

IT **159634-47-6D**, salts **159752-10-0**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(formulation of tablets of growth hormone secretagogues using a wet granulation step)

RN 159634-47-6 HCAPLUS
CN Propanamide, 2-amino-N-[(1R)-2-[1,2-dihydro-1-(methylsulfonyl)spiro[3H-indole-3,4'-piperidin]-1'-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



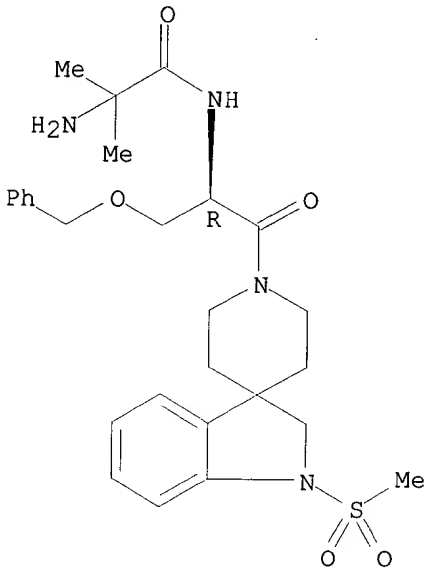
RN 159752-10-0 HCAPLUS
CN Propanamide, 2-amino-N-[(1R)-2-[1,2-dihydro-1-(methylsulfonyl)spiro[3H-indole-3,4'-piperidin]-1'-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl-, monomethanesulfonate (9CI) (CA INDEX NAME)

CM 1

CRN 159634-47-6

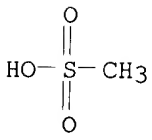
CMF C27 H36 N4 O5 S

Absolute stereochemistry.



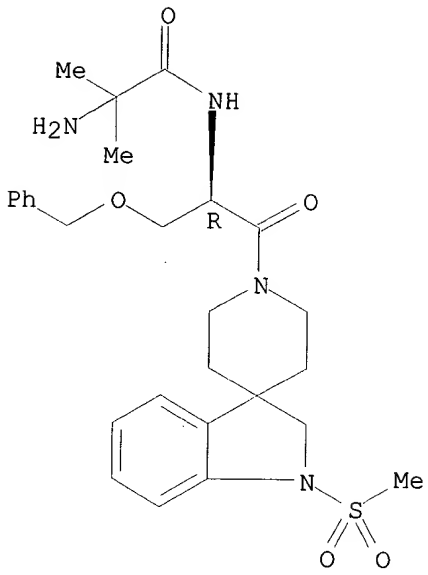
CM 2

CRN 75-75-2
CMF C H4 O3 S



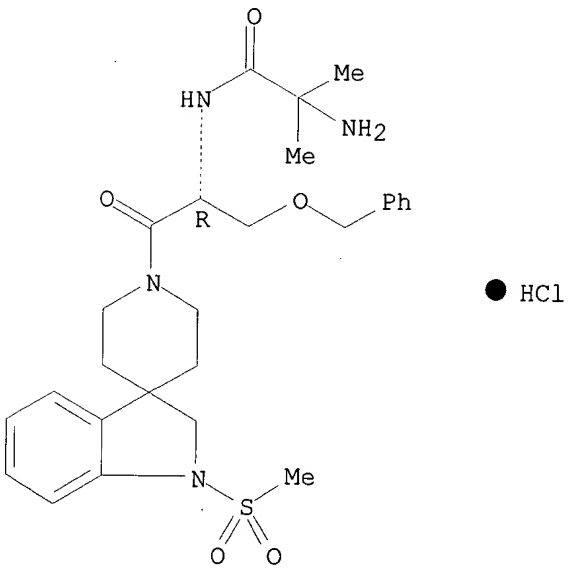
IT **159634-47-6**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prepn. and formulation of; formulation of tablets of growth hormone secretagogues using a wet granulation step)
RN 159634-47-6 HCAPLUS
CN Propanamide, 2-amino-N-[(1R)-2-[1,2-dihydro-1-(methylsulfonyl)spiro[3H-indole-3,4'-piperidin]-1'-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **159633-92-8**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prepn. and reactions in prepn. growth hormone secretagogue; formulation of tablets of growth hormone secretagogues using a wet granulation step)
RN 159633-92-8 HCAPLUS
CN Propanamide, 2-amino-N-[(1R)-2-[1,2-dihydro-1-(methylsulfonyl)spiro[3H-indole-3,4'-piperidin]-1'-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L6 ANSWER 7 OF 22 HCAPLUS COPYRIGHT 2003 ACS on STN
AN 1996:746742 HCAPLUS
DN 126:55085
TI Stimulation of the growth hormone (GH)-insulin-like growth factor I axis by daily oral administration of a GH secretagogue (**MK-**

677) in healthy elderly subjects

AU Chapman, Ian M.; Bach, Mark A.; Van Cauter, Eve; Farmer, Mildred; Krupa, David; Taylor, Alice M.; Schilling, Lisa M.; Cole, Katrina Y.; Skiles, Emily H.; Pezzoli, Suzan S.; Hartman, Mark L.; Veldhuis, Johannes D.; Gormley, Glenn J.; Thorner, Michael O.

CS Dep. Med., Univ. Virginia Health Sci. Cent., Charlottesville, VA, 22908, USA

SO Journal of Clinical Endocrinology and Metabolism (**1996**), 81(12), 4249-4257
CODEN: JCEMAZ; ISSN: 0021-972X

PB Endocrine Society

DT Journal

LA English

CC 2-5 (Mammalian Hormones)

AB Aging is assocd. with declining activity of the GH axis, possibly contributing to adverse body compn. changes and increased incidence of cardiovascular disease. The stimulatory effects on the GH-insulin-like growth factor I (IGF-I) axis of orally administered **MK-677**, a GH-releasing peptide mimetic, were investigated. Thirty-two healthy subjects (15 women and 17 men, aged 64-81 yr) were enrolled in a randomized, double blind, placebo-controlled trial. They received placebo or 2, 10, or 25 mg **MK-677**, orally, once daily for 2 sep. study periods of 14 and 28 days. At baseline and on day 14 of each study period, blood was collected every 20 min for 24 h to measure GH, PRL, and cortisol. Attributes of pulsatile GH release were assessed by 3 independent algorithms. **MK-677** administration for 2 wk increased GH concns. in a dose-dependent manner, with 25 mg/day increasing mean 24-h GH concn. 97.+-.23%. This increase was due to an enhancement of preexisting pulsatile GH secretion. GH pulse height and interpulse nadir concns. increased significantly without significant changes in the no. of pulses. With 25 mg/day **MK-677** treatment, mean serum IGF-I concns. increased into the normal range for young adults (141.+-.21 .mu.g/L at baseline, 219.+-.21 .mu.g/L at 2 wk, and 265.+-.29 .mu.g/L at 4 wk). **MK-677** produced significant increases in fasting glucose (5.4.+-.0.3 to 6.8.+-.0.4 mmol/L at 4 wk) and IGF-binding protein-3. Circulating cortisol concns. did not change, and PRL concns. increased 23%, but remained within the normal range. Once daily treatment of older people with oral **MK-677** for up to 4 wk enhanced pulsatile GH release, significantly increased serum GH and IGF-I concns., and, at a dose of 25 mg/day, restored serum IGF-I concns. to those of young adults.

ST GH IGFI axis elderly **MK677**; growth hormone secretagogue treatment elderly

IT Aging, animal
(elderly; stimulation of GH-insulin-like growth factor I axis by daily oral administration of a GH secretagogue (**MK-677**) in healthy elderly subjects)

IT Aging, animal
(stimulation of GH-insulin-like growth factor I axis by daily oral administration of a GH secretagogue (**MK-677**) in healthy elderly subjects)

IT 9002-72-6, Growth hormone
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(stimulation of GH-insulin-like growth factor I axis by daily oral administration of a GH secretagogue (**MK-677**) in healthy elderly subjects)

IT **159634-47-6, MK-677**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(stimulation of GH-insulin-like growth factor I axis by daily oral

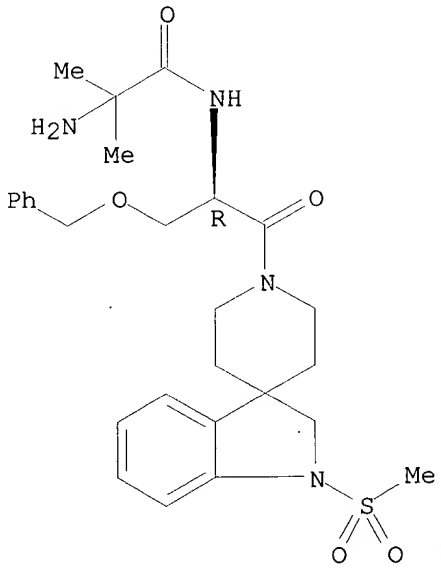
administration of a GH secretagogue (**MK-677**) in healthy elderly subjects)

IT 67763-96-6, Insulin-like growth factor I
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(stimulation of GH-insulin-like growth factor I axis by daily oral administration of a GH secretagogue (**MK-677**) in healthy elderly subjects)

IT **159634-47-6, MK-677**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(stimulation of GH-insulin-like growth factor I axis by daily oral administration of a GH secretagogue (**MK-677**) in healthy elderly subjects)

RN 159634-47-6 HCAPLUS
CN Propanamide, 2-amino-N-[(1R)-2-[1,2-dihydro-1-(methylsulfonyl)spiro[3H-indole-3,4'-piperidin]-1'-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L6 ANSWER 8 OF 22 HCAPLUS COPYRIGHT 2003 ACS on STN
AN 1996:725433 HCAPLUS
DN 126:69945
TI **MK-0677**, a potent, novel, orally active growth hormone (GH) secretagogue: GH, insulin-like growth factor I, and other hormonal responses in beagles
AU Jacks, Thomas; Smith, Roy; Judith, Fred; Schleim, Klaus; Frazier, Easter; Chen, Howard; Krupa, David; Hora, Don, Jr.; Nargund, Ravi; et al.
CS Department Physiology and Biochemistry, Merck Research Laboratories, Rahway, NJ, 07065, USA
SO Endocrinology (**1996**), 137(12), 5284-5289
CODEN: ENDOAO; ISSN: 0013-7227
PB Endocrine Society
DT Journal
LA English
CC 1-10 (Pharmacology)
Section cross-reference(s): 2
AB **MK-0677**, a spiroindoline sulfonamide, is a novel,

orally active GH secretagogue. The effects of **MK-0677** on serum GH and other hormones after oral and i.v. single dose administrations in beagles were evaluated. After oral administration in a balanced eight-dog cross-over study, treatment with **MK-0677** significantly increased peak GH concns., with a 5.3-fold increase (mean, 10.5 ng/mL) at the 0.25 mg/kg dose, a 9.0-fold increase (18.0 ng/mL) at the 0.50 mg/kg dose, and a 15.8-fold increase (31.6 ng/mL) at the 1.0 mg/kg dose. Total GH release, expressed as the area under the curve, showed similar significant increases over the effect of the water placebo. A single oral 1 mg/kg dose in three dogs induced a mean GH peak of 27.6 .+-. 1.5 ng/mL at 120 min, and GH levels remained elevated up to 360 min after treatment. Insulin-like growth factor I (IGF-I) levels were significantly increased by 30% at 480 min after treatment. Cortisol levels were increased 2.4-fold over pretreatment levels. After i.v. administration, compared to the saline control group which had a mean serum GH peak of 3.8 ng/mL, **MK-0677** at 0.25 mg/kg significantly increased peak GH concns. 20.4-fold (77.4 ng/mL). Total GH release, expressed as the area under the curve, showed a similar increase. The mean peak GH level was recorded 10 min after treatment, with GH levels elevated up to 180 min after treatment. IGF-I levels were significantly elevated by 25% at 360 min after the administration of **MK-0677**. Cortisol levels were increased 2.3-fold over pretreatment levels. Insulin and glucose levels were higher, LH and PRL levels were unaltered, and T4 levels were marginally lower; the levels of each of these hormones remained within the normal ranges for dogs throughout the expt. In summary, **MK-0677** is a potent GH secretagogue that induces an immediate, large, long-lasting increase in GH levels when administered orally or i.v. In contrast to GH-releasing peptide-6 and benzolactam secretagogues, GH levels were elevated up to 360 min after treatment, and this was assocd. with a significant increase in IGF-I levels. Cortisol levels were increased; however, the increases were modest compared to those in GH.

ST **MK0677** growth hormone secretagogue; IGF **MK0677** growth hormone

IT **159634-47-6, MK-0677**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(**MK-0677** effect on growth hormone and IGF-I and other hormonal responses in beagles)

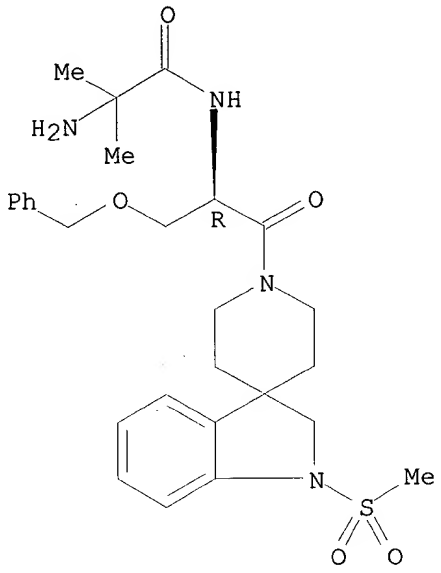
IT 50-23-7, Cortisol 50-99-7, D-Glucose, biological studies 51-48-9, Thyroxine, biological studies 9002-62-4, Prolactin, biological studies 9002-67-9, LH 9002-72-6, Growth hormone 9004-10-8, Insulin, biological studies 67763-96-6, IGF-I
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**MK-0677** effect on growth hormone and IGF-I and other hormonal responses in beagles)

IT **159634-47-6, MK-0677**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(**MK-0677** effect on growth hormone and IGF-I and other hormonal responses in beagles)

RN 159634-47-6 HCAPLUS

CN Propanamide, 2-amino-N-[(1R)-2-[1,2-dihydro-1-(methylsulfonyl)spiro[3H-indole-3,4'-piperidin]-1'-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L6 ANSWER 9 OF 22 HCAPLUS COPYRIGHT 2003 ACS on STN
AN 1996:522032 HCAPLUS
DN 125:186032
TI Solubilization and characterization of a growth hormone secretagogue receptor from porcine anterior pituitary membranes
AU Pomes, Anna; Pong, Sheng-Shung; Schaeffer, James M.
CS Cell Biochem. Physiol., Merck Res. Lab., Rahway, NJ, 07065, USA
SO Biochemical and Biophysical Research Communications (**1996**), 225(3), 939-945
CODEN: BBRCA9; ISSN: 0006-291X
PB Academic
DT Journal
LA English
CC 2-1 (Mammalian Hormones)
AB The discovery of a potential new GH therapy by small mols. that induce GH secretion (GHRP-6, L-692429, **MK-0677**), has increased the interest in these GH secretagogues and their receptor and mechanism of action, which is different from the one of GH-RH. We report the solubilization of the GH-secretagogue-receptor-ligand-G-protein complex (apparent mol. mass of approx. 255 kDa) from porcine anterior pituitary membranes using digitonin, after labeling the receptor with [35S] **MK-0677**. The solubilized receptor showed high affinity (KD = 122.2 pM) and low capacity (Bmax = 3.8 fmol/mg protein). These values and the inhibition consts. (Ki) for a series of GH secretagogues were similar to the values detd. in membranes isolated from porcine anterior pituitary gland. The solubilization of the GH secretagogue receptor opens up the possibility for further mol. characterization and sequencing of the receptor protein, necessary step prior to the identification of the natural ligand that would act as a GH-RH amplifying hormone, and that the GH secretagogues would mimic.
ST growth hormone secretagogue receptor solubilization pituitary
IT Pituitary gland, anterior lobe
(growth hormone secretagogue receptor solubilization and characterization from porcine anterior pituitary membranes)
IT Receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); PUR (Purification or recovery); BIOL (Biological study); PREP (Preparation); PROC (Process)
(somatotropin secretagogue; growth hormone secretagogue receptor

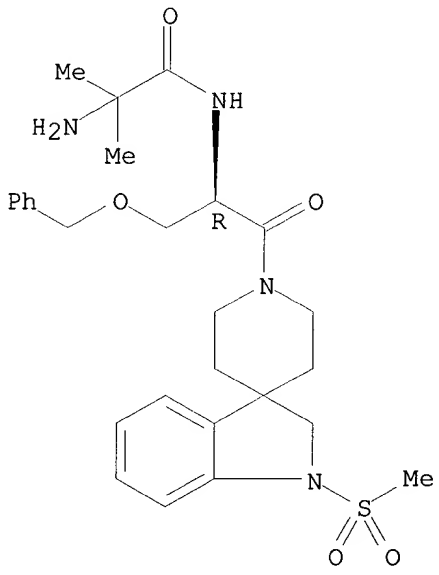
solubilization and characterization from porcine anterior pituitary membranes)

IT 87616-84-0 145455-23-8, L-692429 **159634-47-6, MK-0677**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(growth hormone secretagogue receptor solubilization and characterization from porcine anterior pituitary membranes)

IT **159634-47-6, MK-0677**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(growth hormone secretagogue receptor solubilization and characterization from porcine anterior pituitary membranes)

RN 159634-47-6 HCAPLUS
CN Propanamide, 2-amino-N-[(1R)-2-[1,2-dihydro-1-(methylsulfonyl)spiro[3H-indole-3,4'-piperidin]-1'-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L6 ANSWER 10 OF 22 HCAPLUS COPYRIGHT 2003 ACS on STN
AN 1996:505012 HCAPLUS
DN 125:186060
TI A receptor in pituitary and hypothalamus that functions in growth hormone release
AU Howard, Andrew D.; Feighner, Scott D.; Cully, Doris F.; Arena, Joseph P.; Liberator, Paul A.; Rosenblum, Charles I.; Hamelin, Michel; Hreniuk, Donna L.; Palyha, Oksana C.; et al.
CS Merck Research Labs., Rahway, NJ, 07065, USA
SO Science (Washington, D. C.) (**1996**), 273(5277), 974-977
CODEN: SCIEAS; ISSN: 0036-8075
PB American Association for the Advancement of Science
DT Journal
LA English
CC 2-2 (Mammalian Hormones)
AB Small synthetic mols. termed growth hormone secretagogues (GHSs) act on the pituitary gland and the hypothalamus to stimulate and amplify pulsatile growth hormone (GH) release. A heterotrimeric GTP-binding protein (G protein)-coupled receptor (GPC-R) of the pituitary and arcuate ventromedial and infundibular hypothalamus of swine and humans was cloned

and was shown to be the target of the GHSs. On the basis of its pharmacol. and mol. characterization, this GPC-R defines a neuroendocrine pathway for the control of pulsatile GH release and supports the notion that the GHSs mimic an undiscovered hormone.

ST growth hormone secretagogue receptor sequence; cDNA sequence growth hormone secretagogue receptor; pig growth hormone secretagogue receptor sequence; human growth hormone secretagogue receptor sequence

IT Hypothalamus
Pituitary gland, anterior lobe
Protein sequences
Swine
(growth hormone secretagogue receptor mol. and pharmacol. characterization in pituitary and hypothalamus)

IT Deoxyribonucleic acid sequences
(complementary, growth hormone secretagogue receptor mol. and pharmacol. characterization in pituitary and hypothalamus)

IT 181056-20-2 181056-21-3 181056-22-4 181056-23-5
RL: PRP (Properties)
(amino acid sequence; growth hormone secretagogue receptor mol. and pharmacol. characterization in pituitary and hypothalamus)

IT 87616-84-0 158861-67-7, GHRP 2 **159634-47-6, MK 0677**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(growth hormone secretagogue receptor mol. and pharmacol. characterization in pituitary and hypothalamus)

IT 9002-72-6, Growth hormone
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(growth hormone secretagogue receptor of pituitary and hypothalamus in growth hormone release)

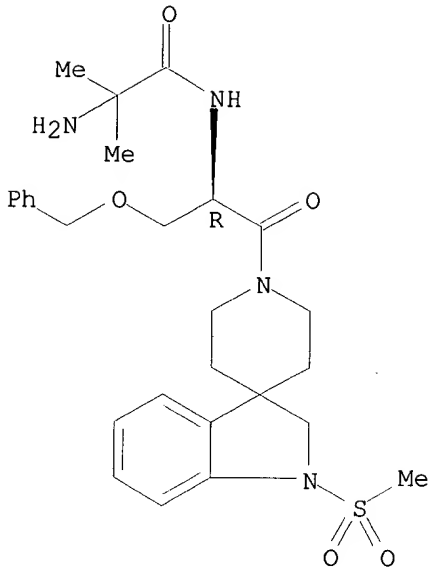
IT 180425-80-3, GenBank U60179 180426-14-6, GenBank U60181 180426-15-7, GenBank U60178 180426-16-8, GenBank U60180
RL: PRP (Properties)
(nucleotide sequence; growth hormone secretagogue receptor mol. and pharmacol. characterization in pituitary and hypothalamus)

IT **159634-47-6, MK 0677**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(growth hormone secretagogue receptor mol. and pharmacol. characterization in pituitary and hypothalamus)

RN 159634-47-6 HCAPLUS

CN Propanamide, 2-amino-N-[(1R)-2-[1,2-dihydro-1-(methylsulfonyl)spiro[3H-indole-3,4'-piperidin]-1'-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L6 ANSWER 11 OF 22 HCAPLUS COPYRIGHT 2003 ACS on STN
AN 1996:491768 HCAPLUS
DN 125:158988
TI Effects of a 7-day treatment with a novel, orally active, growth hormone (GH) secretagogue, **MK-677**, on 24-hour GH profiles, insulin-like growth factor I, and adrenocortical function in normal young men
AU Copinschi, Georges; Van Onderbergen, Anne; L'Hermite-Baleriaux, Mireille; Meendel, Carl M.; Caufriez, Anne; Leproult, Rachel; Bolognese, James A.; De Smet, Marina; Thorner, Michael O.; Van Cauter, Eve
CS Center Study Biological Rhythms and Laboratory Experimental Medicine, Universite Libre de Bruxelles, Brusselsss, B-1070, Belg.
SO Journal of Clinical Endocrinology and Metabolism (**1996**), 81(8), 2776-2782
CODEN: JCEMAZ; ISSN: 0021-972X
PB Endocrine Society
DT Journal
LA English
CC 2-5 (Mammalian Hormones)
Section cross-reference(s): 1
AB To assess the effects of prolonged administration of a novel analog of GH-releasing peptide (**MK-677**), nine healthy young men participated in a randomized, double blind, three-period cross-over comparison of orally administered placebo and 5- and 25-mg doses of **MK-677**. Each period involved bedtime administration of the drug for 7 consecutive days. At the end of each period, plasma levels of insulin-like growth factor I (IGF-I) and IGF-binding protein-3 (IGFBP-3) were measured at 0745 h, and 24-h profiles of plasma GH and cortisol were obtained at 15-min intervals together with the 24-h urinary excretion of free cortisol. Profiles of plasma free cortisol were calcd. at hourly intervals. The amts. of GH secreted were similar in all three conditions, but GH pulse frequency was increased with both dosages of the drug, primarily because of an increase in the no. of low amplitude pulses. Plasma IGF-I levels were increased in a dose-dependent manner, whereas IGFBP-3 levels were increased only with the highest dosage. There was a pos. relation between GH pulse frequency and IGF-I increase. Except for an advance in the nocturnal nadir and in the morning elevation, **MK-677** had no effect on cortisol profiles. In particular, 24-h mean levels of plasma total and free cortisol and urinary excretion of

free cortisol were similar under all conditions. The present data suggest that the use of **MK-677** for the treatment of relative somatotropic deficiency, particularly in older adults compromised by such deficiency, deserves further investigation.

ST growth hormone secretion **MK 677**; IGF blood **MK 677**; cortisol secretion **MK 677**

IT Blood plasma
Urine
(**MK 677** 7-day treatment effect on 24-h growth hormone profiles and IGF-I, and adrenocortical function in normal young men)

IT Glycoproteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(IGF-BP-3 (insulin-like growth factor-binding protein 3), **MK 677** 7-day treatment effect on 24-h growth hormone profiles and IGF-I, and adrenocortical function in normal young men)

IT Rhythm, biological
(circadian, **MK 677** 7-day treatment effect on 24-h growth hormone profiles and IGF-I, and adrenocortical function in normal young men)

IT **159634-47-6, MK-677**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**MK 677** 7-day treatment effect on 24-h growth hormone profiles and IGF-I, and adrenocortical function in normal young men)

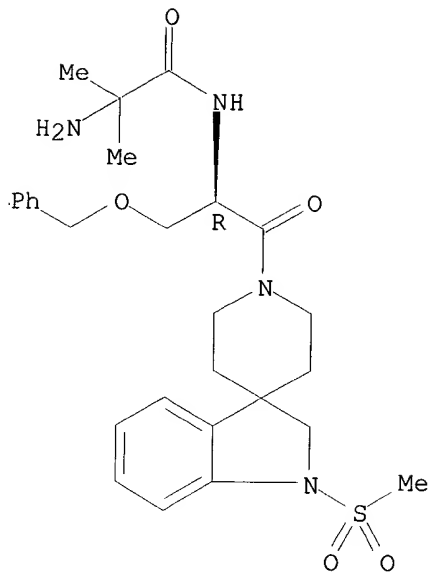
IT 50-23-7, Cortisol 9002-72-6, Growth hormone 67763-96-6, IGF-I
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**MK 677** 7-day treatment effect on 24-h growth hormone profiles and IGF-I, and adrenocortical function in normal young men)

IT **159634-47-6, MK-677**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**MK 677** 7-day treatment effect on 24-h growth hormone profiles and IGF-I, and adrenocortical function in normal young men)

RN 159634-47-6 HCAPLUS

CN Propanamide, 2-amino-N-[(1R)-2-[1,2-dihydro-1-(methylsulfonyl)spiro[3H-indole-3,4'-piperidin]-1'-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L6 ANSWER 12 OF 22 HCAPLUS COPYRIGHT 2003 ACS on STN
AN 1996:469925 HCAPLUS
DN 125:196372
TI Spiro piperidines which promote release of growth hormone
IN Chen, Meng-Hsin; Johnston, David B. R.; Nargund, Ravi P.; Patchett, Arthur A.; Tata, James R.; Yang, Lihu
PA Merck and Co., Inc., USA
SO U.S., 48 pp., Cont.-in-part of U.S. Ser. No. 989, 322, abandoned.
CODEN: USXXAM
DT Patent
LA English
IC ICM A61K031-55
ICS A61K031-44; C07D401-04; C07D451-00
NCL 514215000
CC 34-2 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 2, 18, 63
FAN.CNT 3

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	WO 9413696	A1	19940623	WO 1993-US11038	19931115 <--
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	RW: BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
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	HU 73228	A2	19960729	HU 1995-1681	19931115 <--
	PL 176993	B1	19990831	PL 1993-309331	19931115 <--
	RU 2168512	C2	20010610	RU 1995-113349	19931115 <--
	SK 282166	B6	20011106	SK 1995-759	19931115 <--
	CA 2110670	AA	19940612	CA 1993-2110670	19931203 <--
	CA 2110670	C	20010417		
	CA 2110672	AA	19940612	CA 1993-2110672	19931203 <--
	EP 615977	A1	19940921	EP 1993-309867	19931208 <--
	EP 615977	B1	20020703		
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	AT 220071	E	20020715	AT 1993-309867	19931208 <--
	ES 2177538	T3	20021216	ES 1993-309867	19931208 <--
	AU 9352320	A1	19940623	AU 1993-52320	19931210 <--
	AU 673552	B2	19961114		
	AU 9352321	A1	19940623	AU 1993-52321	19931210 <--
	AU 673017	B2	19961024		
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	JP 2509530	B2	19960619		
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	CN 1034733	B	19970430		
	FI 9502862	A	19950609	FI 1995-2862	19950609 <--
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	NO 9502295	A	19950810	NO 1995-2295	19950609 <--
	US 5652235	A	19970729	US 1996-641311	19960430 <--
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	US 1993-146848		19931103 <--		
	US 1993-147226	A	19931103 <--		
	WO 1993-US11038	W	19931115 <--		
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OS	MARPAT 125:196372				
GI					

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB There are disclosed certain novel compds. identified as spiro piperidines and homologs I and II wherein: R1 = e.g., C1-10 alkyl, aryl, aryl-(C1-6 alkyl); R2 = e.g., H, C1-6 alkyl, C3-7 cycloalkyl; R3a and R3b are independently, e.g., H, halo, C1-6 alkyl; R4 and R5 are independently, H, C1-6 alkyl, substituted C1-6 alkyl where the substituents on alkyl are, e.g., 1 to 5 halo, 1 to 3 hydroxy; R6 is H or C1-6 alkyl; A is (CH2)xCR7R7a(CH2)y or Z(CH2)xCR7R7a(CH2)y wherein x and y are independently 0, 1, 2, or 3; Z is NR2 or O; R7 and R7a are independently, e.g., H, C1-6 alkyl, OR2; B, D, E, and F are independently selected from CR8R10, O, CO, SOm, NR9, wherein one or two of B, D, E, or F may be optionally absent to provide a 5, 6, or 7-membered ring; R8 and R10 are independently, e.g., H, R2, OR2; R9 = e.g., R2, COR2, SO2R2; m is 0, 1, or 2; n is 1 or 2; G, H, I and J are carbon, nitrogen, sulfur or oxygen atoms, such that one or two is a heteroatom, and where one of G, H, I or J may be optionally absent to afford a 5 or 6 membered heterocyclic arom. ring; and the pharmaceutically acceptable salts and individual diastereomers thereof, which promote the release of growth hormone in humans and animals (no data). This property can be utilized to promote the growth of food animals to render the prodn. of edible meat products more efficient, and in humans, to treat physiol. or medical conditions characterized by a deficiency in growth hormone secretion, such as short stature in growth hormone deficient children, and to treat medical conditions which are improved by the anabolic effects of growth hormone. Growth hormone releasing compns. contg. such spiro compds. as the active ingredient thereof are also disclosed. Thus, e.g., 1'-(t-butyloxycarbonyl)spiro[1H-indene-1,4'-piperidine] was subjected to hydroboration/oxidn., to provide 1'-(t-butyloxycarbonyl)-2,3-dihydro-3-oxospiro[1H-indene-1,4'-piperidine]; deprotection followed by trifluoroacetylation afforded the trifluoroacetamide; Schmidt reaction of the latter provided 3,4-dihydro-2-oxospiro[piperidine-4,4'(1H)-quinoline] trifluoroacetamide (together with its spiroisoquinoline isomer); sapon. followed by coupling with .alpha.(R)-[[2-[[(1,1-dimethylethoxy)carbonyl]amino]-2,2-dimethyl-1-oxoethyl]amino]-1H-indole-3-

propanoic acid (prepn. given) and deprotection provided N-[1(R)-[(3,4-dihydro-2-oxospiro[piperidine-4,4'(1H)-quinolin]-1'-yl)carbonyl]-2-(indol-3-yl)ethyl]-2-amino-2-methylpropanamide hydrochloride (III.HCl).

ST spiro piperidine growth hormone secretagogue

IT Spiro compounds
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); FFD (Food or feed use); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(spiro piperidines which promote release of growth hormone)

IT 159633-84-8P 159633-87-1P 159634-19-2P 180465-94-5P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); FFD (Food or feed use); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(spiro piperidines which promote release of growth hormone)

IT 159633-74-6P 159633-75-7P 159633-76-8P 159633-78-0P 159633-79-1P
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159633-90-6P 159633-91-7P **159633-92-8P** 159633-94-0P
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180466-14-2P 180582-78-9P 180693-14-5P 180693-16-7P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); FFD (Food or feed use); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(spiro piperidines which promote release of growth hormone)

IT 9002-72-6, Growth hormone
RL: BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study)
(spiro piperidines which promote release of growth hormone)

IT 55-86-7, Mechlorethamine hydrochloride 58-85-5, Biotin 98-09-9, Benzenesulfonyl chloride 100-39-0, Benzyl bromide 109-04-6, 2-Bromopyridine 501-53-1 1569-69-3, Cyclohexyl mercaptan 4048-33-3, 6-Amino-1-hexanol 4377-33-7, 2-Picolyl chloride 5241-64-5 5342-91-6 6320-02-1, 2-Bromothiophenol 6368-20-3, BOC-D-serine 10147-37-2, Isopropylsulfonyl chloride 15186-48-8 24424-99-5, Di-tert-butyl dicarbonate 30992-29-1 35356-70-8, Methyl 2-acetamidoacrylate 37663-44-8 37663-46-0 47173-80-8 56146-83-9 65915-94-8 69584-87-8, 2,5-Difluorophenylacetonitrile 69584-91-4 75930-65-3 79099-07-3 82732-07-8 85118-00-9, 2,6-Difluorobenzyl bromide 96602-46-9 102830-49-9 115509-01-8 136080-19-8 136081-84-0 136081-93-1 137419-24-0 149270-12-2 156130-68-6 159634-89-6 159635-35-5 159635-36-6 159635-37-7 159635-38-8 159635-39-9 159635-46-8 159635-50-4 180465-68-3 180466-16-4
RL: RCT (Reactant); RACT (Reactant or reagent)
(spiro piperidines which promote release of growth hormone)

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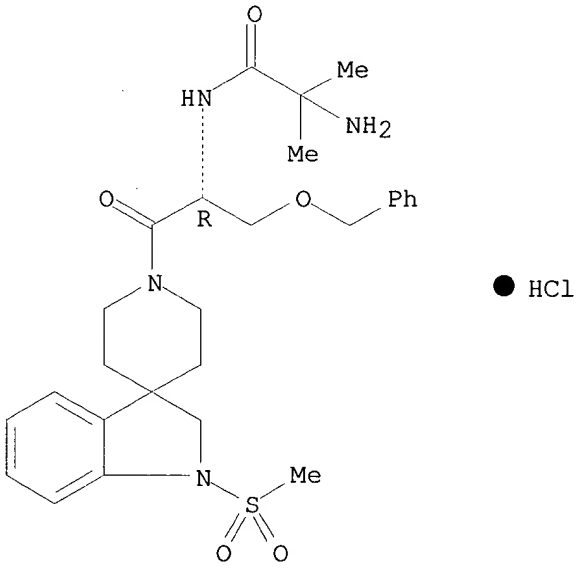
180466-10-8P 180466-11-9P 180466-12-0P 180466-15-3P 180693-15-6P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(spiro piperidines which promote release of growth hormone)

IT **159633-92-8P 159634-47-6P 159752-10-0P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); FFD (Food or feed use); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(spiro piperidines which promote release of growth hormone)

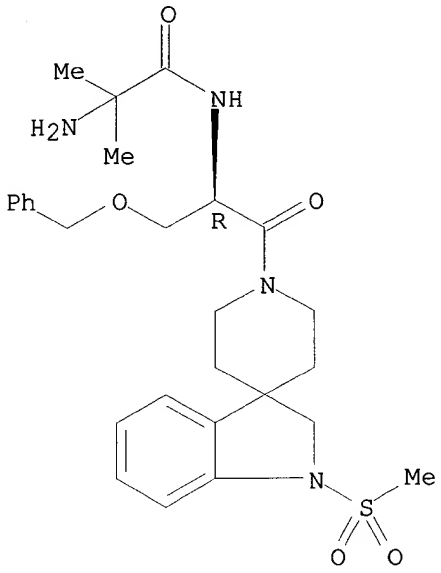
RN 159633-92-8 HCAPLUS
CN Propanamide, 2-amino-N-[(1R)-2-[1,2-dihydro-1-(methylsulfonyl)spiro[3H-indole-3,4'-piperidin]-1'-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 159634-47-6 HCAPLUS
CN Propanamide, 2-amino-N-[(1R)-2-[1,2-dihydro-1-(methylsulfonyl)spiro[3H-indole-3,4'-piperidin]-1'-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

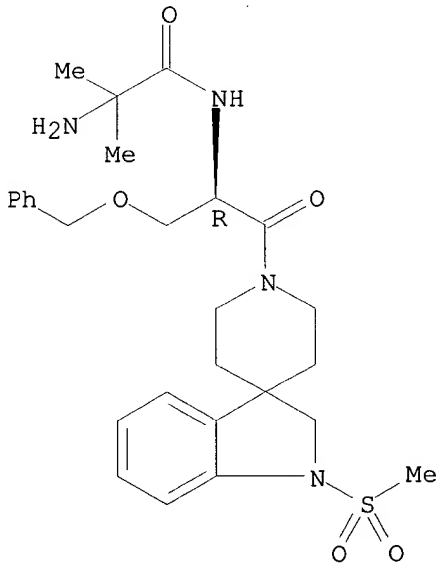


RN 159752-10-0 HCAPLUS
CN Propanamide, 2-amino-N-[(1R)-2-[1,2-dihydro-1-(methylsulfonyl)spiro[3H-indole-3,4'-piperidin]-1'-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl-, monomethanesulfonate (9CI) (CA INDEX NAME)

CM 1

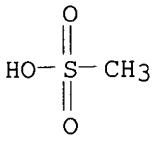
CRN 159634-47-6
CMF C27 H36 N4 O5 S

Absolute stereochemistry.

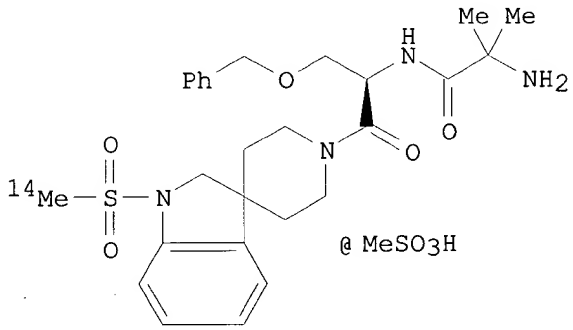


CM 2

CRN 75-75-2
CMF C H4 O3 S



L6 ANSWER 13 OF 22 HCAPLUS COPYRIGHT 2003 ACS on STN
AN 1996:423805 HCAPLUS
DN 125:195402
TI Synthesis, stability, and radiolytic decomposition of carbon-14 labeled **MK0677**
AU Jones, Allen N.; Dean, Dennis C.; Jenkins, Herbert J.; Melillo, David G.; Nargund, Ravi P.; Wallace, Michael A.
CS Drug Metabolism II, Merck Res. Lab., Rahway, NJ, 07065, USA
SO Journal of Labelled Compounds & Radiopharmaceuticals (**1996**), 38(6), 561-565
CODEN: JLCRD4; ISSN: 0362-4803
PB Wiley
DT Journal
LA English
CC 27-20 (Heterocyclic Compounds (One Hetero Atom))
GI



I

AB **MK0677** is an orally active growth hormone secretagogue. The crystd. carbon-14 labeled material, I, was found to undergo radiolytic decompn. via a peroxide intermediate which resulted in loss of the benzyl group. The rate was diminished when the tracer was crystd. from nitrogen-degassed solvents. Storage stability was best in aq. ethanol.
ST **MK0677** carbon 14 prepn stability decompn
IT 159635-06-0
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn., stability, and radiolytic decompn. of C-14 labeled **MK0677**)
IT 84614-43-7P 84627-46-3P, Methane-14C-sulfonyl chloride 180985-77-7P 180985-79-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn., stability, and radiolytic decompn. of C-14 labeled **MK0677**)
IT 180985-80-2P 180985-81-3P
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn., stability, and radiolytic decompn. of C-14 labeled **MK0677**)

L6 ANSWER 14 OF 22 HCAPLUS COPYRIGHT 2003 ACS on STN
AN 1996:414659 HCAPLUS
TI Design and biological activities of aryl piperazine-based growth hormone secretagogues.
AU Barakat, Khaled J.; Nargund, Ravi P.; Prendergast, Kristine J.; Cheng, Kang; Jacks, Thomas M.; Schleim, Klaus; Chan, Wanda W. -S.; Butler, Bridger; Fraizier, Easter; et al.
CS Department Medical Chemistry, Merck Research Laboratories, Rahway, NJ, 07065, USA
SO Book of Abstracts, 212th ACS National Meeting, Orlando, FL, August 25-29 (**1996**), MEDI-071 Publisher: American Chemical Society, Washington, D. C.
CODEN: 63BFAF
DT Conference; Meeting Abstract
LA English
AB Growth hormone (GH) secretagogues of peptidyl and peptidomimetic designs, including **MK-0677**, are being evaluated clin. as potential alternatives for GH replacement therapy. SAR studies in the **MK-0677** series have led to the discovery of a novel class of potent aryl piperazine-based GH secretagogues exemplified by L-163,689 (ED50=6.3nM). The design, synthesis and biol. properties of this new class of GH secretagogues will be presented.

L6 ANSWER 15 OF 22 HCAPLUS COPYRIGHT 2003 ACS on STN
AN 1996:414598 HCAPLUS
TI The design and synthesis of orally active short duration spiroindane growth hormone secretagogues
AU Tata, James R.; Lu, Zhijian; Cheng, Kang; Wei, Liente; Chan, Wanda W. -S.; Butler, Bridget; Schleim, Klaus D.; Jacks, Thomas M.; Leung, Kwan; et al.
CS Department Medicinal Chemistry, Merck Research Laboratories, Rahway, NJ, 07065, USA
SO Book of Abstracts, 212th ACS National Meeting, Orlando, FL, August 25-29 (**1996**), MEDI-010 Publisher: American Chemical Society, Washington, D. C.
CODEN: 63BFAF
DT Conference; Meeting Abstract
LA English
AB The clin. efficacy and specificity of growth hormone secretagogues has been established for both peptide (GHPR-6) and nonpeptide (L-692,429) secretagogues. Our current clin. candidate **MK-0677** has a long duration of action. In order to investigate the relationship between duration of action and the release of GH and IGF-1, an orally active short duration secretagogue was desired. Incorporation of an ester into the benzylic position of the spiroindane secretagogues provided a dramatic increase in potency, and good oral activity along with a short duration of action. The best compd. in this series, L-163,833, has an EC50 of 1 nM in the rat pituitary cell assay and elevates GH in dogs after oral doses as low as 0.25 mg / kg. SAR studies of these ester-contg. secretagogues along with relevent in vivo data will be presented.

L6 ANSWER 16 OF 22 HCAPLUS COPYRIGHT 2003 ACS on STN
AN 1996:414597 HCAPLUS
TI Novel probes derived from **MK-0677** for characterization of the growth hormone secretagogue receptor.
AU Nargund, Ravi P.; Feighner, Scott; Hrenuik, Donna; Dashkevicz, Michael; Cheng, Kang; Chan, Wanda W. -S.; Van Der Ploeg, Lex H. T.; Smith, Roy G.; Patchett, Arthur A.
CS Merck Research Laboratories, Rahway, NJ, 07065, USA
SO Book of Abstracts, 212th ACS National Meeting, Orlando, FL, August 25-29 (**1996**), MEDI-009 Publisher: American Chemical Society, Washington, D. C.
CODEN: 63BFAF
DT Conference; Meeting Abstract

LA English
AB **MK-0677** (Proc. Natl. Acad. Sci. 1995, 92, 7001) is a novel, orally active growth hormone (GH) secretagogue that is being evaluated clin. as a potential alternative to GH replacement therapy. In animals and in the clinic GH secretagogues, including **MK-0677**, induce a physiol.-relevant pulsatile release of GH. The mechanisms by which the secretagogues cause the release of GH in vivo are not clearly understood. To assist in this effort, we synthesized highly active biotinylated, fluorophore-conjugated and photoaffinity probes that were useful in identifying a new G-protein coupled receptor, the GH secretagogue receptor that is linked to the activity of these secretagogues. These studies have shed new light on our understanding of the neuroendocrine regulation of pulsatile GH secretion. Findings from SAR studies around the sulfonamide unit of **MK-0677**, including the design, synthesis and biol. properties of these novel probes with results from receptor studies will be presented.

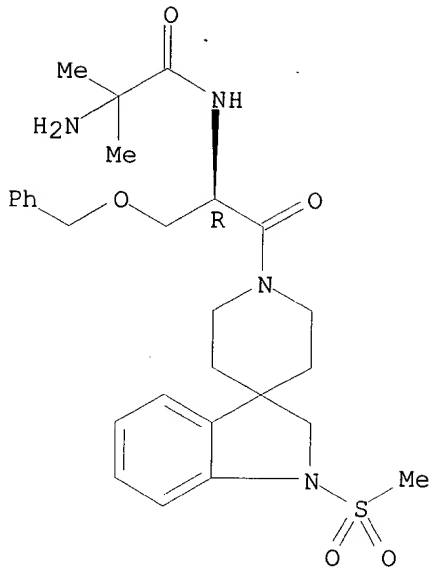
L6 ANSWER 17 OF 22 HCAPLUS COPYRIGHT 2003 ACS on STN
AN 1996:210122 HCAPLUS
DN 124:311674
TI Development of a High Specific Activity Sulfur-35-Labeled Sulfonamide Radioligand That Allowed the Identification of a New Growth Hormone Secretagogue Receptor
AU Dean, Dennis C.; Nargund, Ravi P.; Pong, Sheng-Shung; Chaung, Lee-Yuh P.; Griffin, Patrick; Melillo, David G.; Ellsworth, Robert L.; Van Der Ploeg, Lex H. T.; Patchett, Arthur A.; Smith, Roy G.
CS Department of Drug Metabolism, Merck Co., Rahway, NJ, 07065, USA
SO Journal of Medicinal Chemistry (**1996**), 39(9), 1767-70
CODEN: JMCMAR; ISSN: 0022-2623
PB American Chemical Society
DT Journal
LA English
CC 9-15 (Biochemical Methods)
Section cross-reference(s): 2, 28, 34
AB A high specific activity (.apprx.1000 Ci/mmol) sulfur-35 labeled radioligand, [35S]**MK-0677**, was prepd. which allowed characterization of a newly discovered receptor for peptide and non-peptide growth hormone secretagogues. As an alternative to unacceptable iodine-125 derivatization, a [35S]sulfonamide was formed from reaction of an amine with methane[35S]sulfonyl chloride. The near theor. specific activity methane[35S]sulfonic acid used to prep. this reagent was obtained by in situ trapping of unstable sodium [35S]sulfite with Me iodide. Details of the process which allow efficient synthesis of highly radiochem. pure and stable [35S]sulfonamide radioligand from [35S]sulfuric acid are presented. Utilization of this optimally selective and sensitive probe revealed high affinity binding sites (KD = 161 .+-. 11 pM) in porcine and rat anterior pituitary membranes which are present in extremely low concn. (Bmax = 2.5-7.0 fmol/mg of protein).
ST spiropyridine analog growth hormone receptor prepn; sulfur 35 spiropyridine analog prepn
IT Receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(somatotropin, prepn. of sulfur-35-labeled sulfonamide radioligand for identification of growth hormone secretagogue receptor)
IT 176178-27-1P
RL: ARG (Analytical reagent use); PRP (Properties); SPN (Synthetic preparation); ANST (Analytical study); PREP (Preparation); USES (Uses)
(prepn. of sulfur-35-labeled sulfonamide radioligand for identification of growth hormone secretagogue receptor)
IT 23680-31-1 69584-91-4
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of sulfur-35-labeled sulfonamide radioligand for identification

of growth hormone secretagogue receptor)

IT 159635-06-0P 167483-91-2P 176178-26-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of sulfur-35-labeled sulfonamide radioligand for identification of growth hormone secretagogue receptor)

L6 ANSWER 18 OF 22 HCAPLUS COPYRIGHT 2003 ACS on STN
AN 1996:37774 HCAPLUS
DN 124:107140
TI Identification of a new G-protein-linked receptor for growth hormone secretagogues
AU Pong, Sheng-Shung; Chaung, Lee-Yuh P.; Dean, Dennis C.; Nargund, Ravi P.; Patchett, Arthur A.; Smith, Roy G.
CS Department Biochemistry and Physiology, Merck Research Laboratories, Rahway, NJ, 07065, USA
SO Molecular Endocrinology (**1996**), 10(1), 57-61
CODEN: MOENEN; ISSN: 0888-8809
PB Endocrine Society
DT Journal
LA English
CC 2-5 (Mammalian Hormones)
AB The potential application of small mols. in GH therapy has recently become a topic of increasing interest. The spiroindoline **MK-0677**, the benzolactam L-692,429, and the peptides, GHRP-6 and hexarelin, have been shown to possess potent and selective GH-secretory activity in several species including human. Moreover, these synthetic GH secretagogues act on a signal transduction pathway distinct from that of GHRH. A specific high affinity binding site in porcine and rat anterior pituitary membranes that mediates the activity of these secretagogues has now been identified. The binding affinity of these structurally diverse secretagogues is tightly correlated with GH-secretory activity. The binding is Mg2+-dependent, is inhibited by GTP-.gamma.-S, and is not displaced by GHRH and somatostatin. The receptor is distinct from that for GHRH and has the properties of a new G-protein-coupled receptor. It is speculated that these GH secretagogues mimic an unidentified natural hormone that regulates GH secretion in concert with GHRH and somatostatin.
ST G protein linked receptor GH secretagogue
IT Receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(G protein-coupled; identification of a new G-protein-linked receptor for growth hormone secretagogues)
IT 7439-95-4, Magnesium, biological studies 87616-84-0 140703-51-1, Hexarelin 145455-23-8, L-692429 145455-35-2, L-692585 145456-68-4, L 692428 **159634-47-6, MK 0677**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(identification of a new G-protein-linked receptor for growth hormone secretagogues)
IT **159634-47-6, MK 0677**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(identification of a new G-protein-linked receptor for growth hormone secretagogues)
RN 159634-47-6 HCAPLUS
CN Propanamide, 2-amino-N-[(1R)-2-[1,2-dihydro-1-(methylsulfonyl)spiro[3H-indole-3,4'-piperidin]-1'-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L6 ANSWER 19 OF 22 HCAPLUS COPYRIGHT 2003 ACS on STN
AN 1996:8901 HCAPLUS
DN 124:46081
TI Induction of c-fos mRNA in the arcuate nucleus of normal and mutant growth hormone-deficient mice by a synthetic non-peptidyl growth hormone secretagogue
AU Sirinathsinghji, D. J. S.; Chen, H. Y.; Hopkins, R.; Trumbauer, M.; Heavens, R.; Rigby, M.; Smith, R. G.; Van der Ploeg, L. H. T.
CS Merck Sharp and Dohme Research Laboratories, Neuroscience Research Centre, Harlow Essex, CM20 2QR, UK
SO NeuroReport (**1995**), 6(15), 1989-92
CODEN: NERPEZ; ISSN: 0959-4965
PB Rapid Science Publishers
DT Journal
LA English
CC 2-5 (Mammalian Hormones)
AB The authors have studied by in situ hybridization histochem. the mRNA expression of the c-fos immediate early gene in the brains of wild type and dwarf (dw/dw) and little (lit/lit) mutant-mice after systemic injections of the synthetic GH secretagogues GHRP-6 and **L-163,191**. Both GH secretagogues induced a marked c-fos mRNA expression in the arcuate-ventromedial hypothalamus (ARC-VMH) of both control and mutant mice indicating a possible action on growth hormone releasing hormone (GHRH) neurons in the ARC-VMH. Both dw/dw and lit/lit mice showed a 5-fold elevation in GHRH mRNA expression in the ARC-VMH compared with control animals under basal conditions. Since lit/lit mice have a reduced ability to secrete GH and lack a functional GHRH receptor while dw/dw mice lack both GH and presumably GHRH receptors, the GH-secretagogue-induced c-fos mRNA in the brain of these mutants are unlikely to be mediated by an indirect action of GH or a interaction of the synthetic GH-secretagogue with the GHRH receptor.
ST cfos hypothalamus GH secretagogue
IT Hypothalamus
(arcuate nucleus, induction of c-fos mRNA in the arcuate nucleus of normal and mutant growth hormone-deficient mice by a synthetic non-peptidyl growth hormone secretagogue)
IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(c-fos, induction of c-fos mRNA in the arcuate nucleus of normal and mutant growth hormone-deficient mice by a synthetic non-peptidyl growth hormone secretagogue)

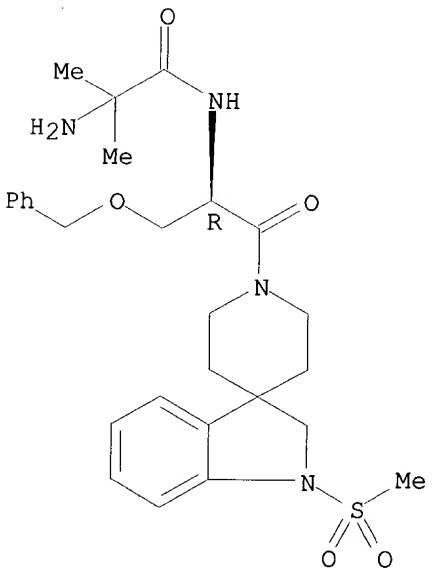
IT Ribonucleic acid formation factors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(gene c-fos, induction of c-fos mRNA in the arcuate nucleus of normal and mutant growth hormone-deficient mice by a synthetic non-peptidyl growth hormone secretagogue)

IT 87616-84-0 **159634-47-6, L 163191**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(induction of c-fos mRNA in the arcuate nucleus of normal and mutant growth hormone-deficient mice by a synthetic non-peptidyl growth hormone secretagogue)

IT **159634-47-6, L 163191**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(induction of c-fos mRNA in the arcuate nucleus of normal and mutant growth hormone-deficient mice by a synthetic non-peptidyl growth hormone secretagogue)

RN 159634-47-6 HCAPLUS
CN Propanamide, 2-amino-N-[(1R)-2-[1,2-dihydro-1-(methylsulfonyl)spiro[3H-indole-3,4'-piperidin]-1'-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L6 ANSWER 20 OF 22 HCAPLUS COPYRIGHT 2003 ACS on STN
AN 1995:924276 HCAPLUS
TI The discovery of **L-163,191** (**MK-0677**): A Potent, orally active growth hormone secretagogue.
AU Nargund, Ravi P.; Patchett, Arthur A.; Barakat, Khaled J.; Tata, James R.; Chen, Meng-Hsin; Johnston, David B. R.; Cheng, Kang; Jacks, Thomas M.; Schleim, Klaus; et al.
CS Medicinal Chemistry, Merck Research Laboratories, Rahway, NJ, 07065, USA
SO Book of Abstracts, 210th ACS National Meeting, Chicago, IL, August 20-24 (**1995**), Issue Pt. 2, MEDI-012 Publisher: American Chemical Society, Washington, D. C.
CODEN: 61XGAC

DT Conference; Meeting Abstract
LA English
AB Interest in growth hormone secretagogues (GH) has intensified in the last several years based on promising, ever-widening investigational applications of recombinant growth hormone (rGH) in animals and in humans. Two classes of GH secretagogues have been reported in the literature. These include the growth hormone releasing peptides (GHRPs) and the non-peptide benzolactam biphenyl tetrazoles (L-692,429). Unfortunately, L-692,429 and the GHRPs have been reported to have poor oral bioavailability. Our efforts to identify potent, orally active growth hormone secretagogues have culminated in the discovery of the clin. candidate **L-163,191** (**MK-0677**). **L-163,191** is a structurally distinct GH secretagogue. **L-163,191** releases GH from rat pituitary cells with an EC50=1.3 .+-. 0.09nM, elevates GH in lab. animals following oral doses as low as 0.125mg/kg and was shown to be specific in its release of GH without significant effect on other measured pituitary hormones. The design and biol. activities of **L-163,191** will be discussed.

L6 ANSWER 21 OF 22 HCAPLUS COPYRIGHT 2003 ACS on STN
AN 1995:700762 HCAPLUS
DN 123:160569
TI Design and biological activities of **L-163,191** (**MK-0677**): a potent, orally active growth hormone secretagogue
AU Patchett, A. A.; Nargund, R. P.; Tata, J. R.; Chen, M.-H.; Barakat, K. J.; Johnston, D. B. R.; Cheng, K.; Chan, W. W.-S.; Butler, B.; et al.
CS Dep. Med. Chem., Merck Res. Lab., Rahway, NJ, 07065-0900, USA
SO Proceedings of the National Academy of Sciences of the United States of America (**1995**), 92(15), 7001-5
CODEN: PNASA6; ISSN: 0027-8424
PB National Academy of Sciences
DT Journal
LA English
CC 1-10 (Pharmacology)
Section cross-reference(s): 2
AB A potent, orally active growth hormone (GH) secretagogue **L-163,191** belonging to a recently synthesized structural class has been characterized. **L-163,191** releases GH from rat pituitary cells in culture with EC50 = 1.3 nM and is mechanistically indistinguishable from the GH-releasing peptide GHRP-6 and the prototypical nonpeptide GH secretagogue L-692,429 but clearly distinguishable from the natural GH secretagogue, GH-releasing hormone. **L-163,191** elevates GH in dogs after oral doses as low as 0.125 mg/kg and was shown to be specific in its release of GH without significant effect on plasma levels of aldosterone, LH, thyroxine, and prolactin after oral administration of 1 mg/kg. Only modest increases in cortisol were obsd. Based on these properties, **L-163,191** has been selected for clin. studies.
ST **L163191** growth hormone secretagogue
IT **159634-47-6, L 163191**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(design and biol. activities of **L-163,191** (**MK-0677**) as a potent, orally active growth hormone secretagogue)
IT 9002-72-6, Growth hormone
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(design and biol. activities of **L-163,191** (**MK-0677**) as a potent, orally active growth hormone

secretagogue)

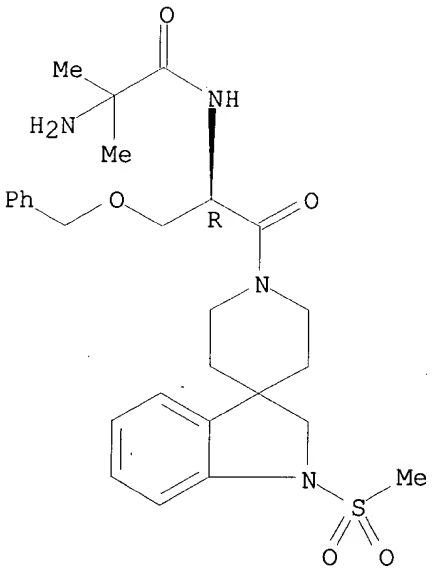
IT 159634-42-1P 159634-43-2P 167386-16-5P 167386-17-6P 167386-18-7P
167386-19-8P 167386-20-1P 167386-21-2P 167386-22-3P 167386-23-4P
167386-24-5P **167386-25-6P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. and biol. activities of analogs of the nonpeptidyl L-692-429 growth hormone secretagogue)

IT **159634-47-6, L 163191**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(design and biol. activities of **L-163,191** (**MK-0677**) as a potent, orally active growth hormone secretagogue)

RN 159634-47-6 HCAPLUS

CN Propanamide, 2-amino-N-[(1R)-2-[1,2-dihydro-1-(methylsulfonyl)spiro[3H-indole-3,4'-piperidin]-1'-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

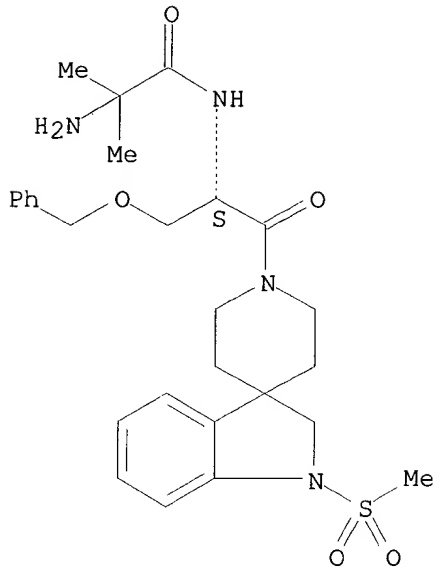


IT **167386-25-6P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. and biol. activities of analogs of the nonpeptidyl L-692-429 growth hormone secretagogue)

RN 167386-25-6 HCAPLUS

CN Propanamide, 2-amino-N-[2-[1,2-dihydro-1-(methylsulfonyl)spiro[3H-indole-3,4'-piperidin]-1'-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl-, (S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L6 ANSWER 22 OF 22 HCAPLUS COPYRIGHT 2003 ACS on STN
AN 1995:511384 HCAPLUS
DN 122:213945
TI Spiro piperidines and homologs which promote release of growth hormone
IN Chen, Meng-Hsin; Johnston, David B. R.; Nargund, Ravi P.; Patchett, Arthur A.; Tata, James R.; Yang, Lihu
PA Merck and Co., Inc., USA
SO PCT Int. Appl., 155 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C07K005-02
ICS C07K005-06; C07D471-10; A61K037-02; A61K031-445
CC 27-17 (Heterocyclic Compounds (One Hetero Atom))
Section cross-reference(s): 34
FAN.CNT 3

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	RW: BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG						
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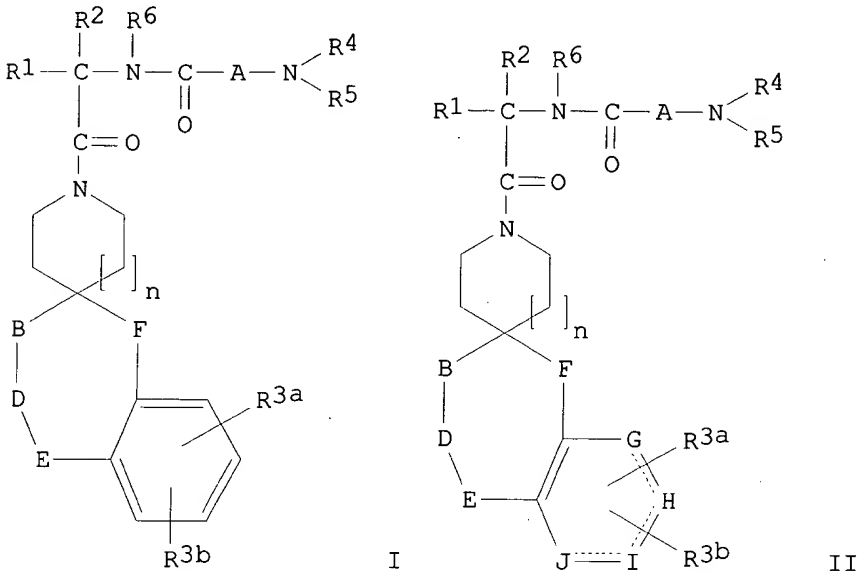

I II

AB The title compds. [I; A = (un)substituted alkylene; B, D, E, F = (un)substituted CH2, O, C:O, S(O)m, etc.; m = 0-2; R1 = (un)substituted alkyl, aryl, cycloalkyl, etc.;, R2 = H, C1-6 alkyl, C3-7 cycloalkyl; R3a, R3b = H, halogen, C1-6 alkyl, OR2, CN, etc.; R4, R5 = H, (un)substituted C1-6 alkyl; R6 = H, C1-6 alkyl; n = 1, 2], [II; G, H, I, J = C, N, S, O], which promote the release of growth hormone (no data), are prepd. Thus, N-[1(R)-[(2',3'-dihydro-2-oxo-spiro[piperidine-4,4'(H)-quinolin]-1-yl)carbonyl]-2-(indol-3-yl)ethyl]-2-amino-2-methylpropanamide hydrochloride was prepd. in 7 steps from 1'-(tert-butyloxycarbonyl)spiro[1H-indene-1,4'-piperidine].

ST dihydrooxospiropiperidinequinonlinylcarbonylindolylethylaminomethylpropanamide prepn growth hormone release; quinoline spiro growth hormone release

IT 159634-42-1 159634-43-2 159634-44-3 159634-45-4 159634-46-5
159634-47-6 159634-49-8 159634-50-1 159634-51-2
159634-52-3 159634-53-4 159634-54-5 159634-55-6 159634-56-7
159634-57-8 159634-58-9
RL: RCT (Reactant); RACT (Reactant or reagent)
(growth hormone release promoter)

IT 171-75-5P 37751-73-8P 147372-85-8P 154731-88-1P 159634-59-0P
159634-60-3P 159634-61-4P 159634-62-5P 159634-63-6P 159634-64-7P
159634-65-8P 159634-66-9P 159634-67-0P 159634-68-1P 159634-69-2P
159634-70-5P 159634-71-6P 159634-72-7P 159634-73-8P 159634-74-9P
159634-75-0P 159634-76-1P 159634-77-2P 159634-78-3P 159634-79-4P
159634-80-7P 159634-81-8P 159634-82-9P 159634-83-0P 159634-84-1P
159634-86-3P 159634-87-4P 159634-88-5P 159634-89-6P 159634-91-0P
159634-92-1P 159634-93-2P 159634-94-3P 159634-95-4P 159634-96-5P
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159635-02-6P 159635-03-7P 159635-04-8P 159635-05-9P 159635-06-0P
159635-07-1P 159635-09-3P 159635-11-7P 159635-12-8P 159635-13-9P
159635-14-0P 159635-15-1P 159635-18-4P 159635-19-5P 159635-22-0P
159635-23-1P 159635-24-2P 159635-25-3P 159635-26-4P 159635-27-5P
159635-28-6P 159635-29-7P 159635-30-0P 159635-31-1P 159635-32-2P
159635-49-1P 180465-95-6P 180465-96-7P 180466-02-8P 180466-03-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and reaction of, in prepn. of growth hormone release promoters)

IT 66376-36-1P, Alendronate
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of)

IT 159635-40-2P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of, as growth hormone release promoter)

IT 159633-74-6P 159633-75-7P 159633-76-8P 159633-77-9P 159633-78-0P
159633-79-1P 159633-80-4P 159633-81-5P 159633-82-6P 159633-83-7P
159633-84-8P 159633-85-9P 159633-86-0P 159633-87-1P 159633-88-2P
159633-89-3P 159633-90-6P 159633-91-7P **159633-92-8P**
159633-94-0P 159633-95-1P 159633-96-2P 159633-97-3P 159633-98-4P
159633-99-5P 159634-01-2P 159634-03-4P 159634-04-5P 159634-06-7P
159634-07-8P 159634-08-9P 159634-09-0P 159634-10-3P 159634-12-5P
159634-13-6P 159634-14-7P 159634-16-9P 159634-18-1P 159634-19-2P
159634-20-5P 159634-21-6P 159634-23-8P 159634-24-9P 159634-26-1P
159634-33-0P 159634-35-2P 159634-36-3P 159634-37-4P 159634-38-5P
159634-39-6P 159634-41-0P 159634-48-7P 159634-85-2P 159634-90-9P
159635-41-3P **159752-10-0P** 180465-98-9P 180466-01-7P
180466-05-1P 180466-06-2P
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, for growth hormone release promotion)

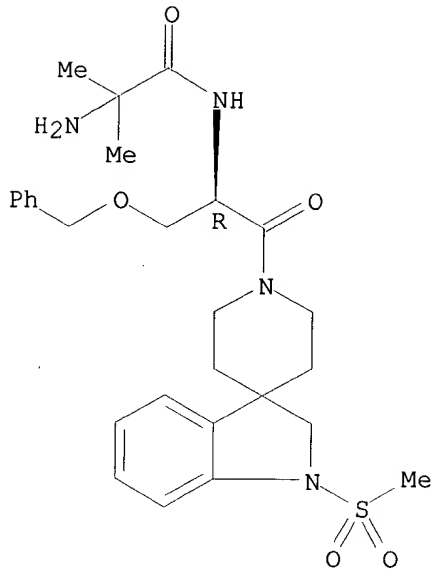
IT 12629-01-5, Human growth hormone
RL: RCT (Reactant); RACT (Reactant or reagent)
(promoters for release of, spiropiperidines and homologs as)

IT 55-86-7 58-85-5, Biotin 75-91-2, tert-Butyl hydroperoxide 100-39-0, Benzyl bromide 109-04-6, 2-Bromopyridine 358-23-6, Triflic anhydride 3164-85-0, Potassium 2-ethylhexanoate 3850-40-6 4377-33-7, 2-Picolyl chloride 5241-64-5 6320-02-1, 2-Bromothiophenol 6368-20-3
14347-78-5 30992-29-1 35356-70-8, Methyl 2-acetamidoacrylate
37663-44-8 50893-53-3, 1-Chloroethyl chloroformate 56146-83-9
69584-87-8, 2,5-Difluorophenylacetonitrile 69584-91-4 75930-65-3
79099-07-3 82732-07-8 85118-00-9, 2,6-Difluorobenzyl bromide
86778-91-8 96602-46-9 102830-49-9 115509-01-8 136081-84-0
136081-93-1 137419-24-0 141527-78-8 150009-60-2 159634-86-3
159634-94-3 159634-97-6 159635-27-5 159635-33-3 159635-34-4
159635-35-5 159635-36-6 159635-37-7 159635-38-8 159635-39-9
159635-43-5 159635-44-6 159635-45-7 159635-46-8 159635-47-9
159635-50-4 159635-51-5 186706-80-9
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, in prepn. of growth hormone release promoters)

IT **159634-47-6**
RL: RCT (Reactant); RACT (Reactant or reagent)
(growth hormone release promoter)

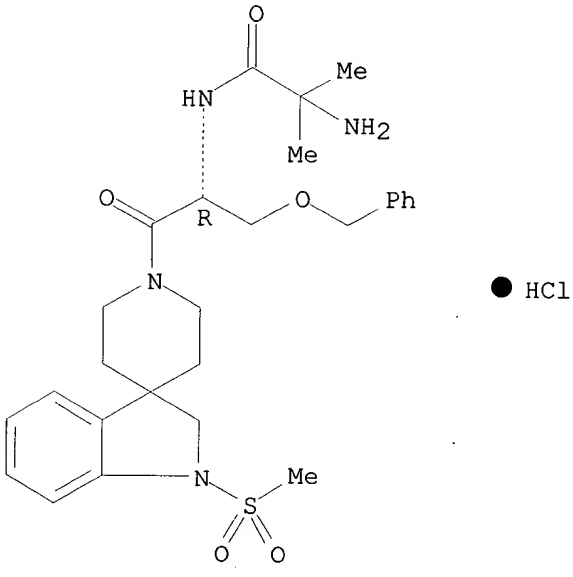
RN 159634-47-6 HCAPLUS
CN Propanamide, 2-amino-N-[(1R)-2-[1,2-dihydro-1-(methylsulfonyl)spiro[3H-indole-3,4'-piperidin]-1'-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **159633-92-8P 159752-10-0P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, for growth hormone release promotion)
RN 159633-92-8 HCAPLUS
CN Propanamide, 2-amino-N-[(1R)-2-[1,2-dihydro-1-(methylsulfonyl)spiro[3H-indole-3,4'-piperidin]-1'-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.



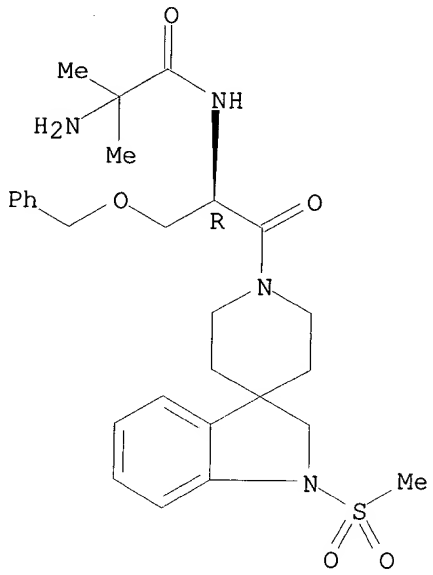
RN 159752-10-0 HCAPLUS
CN Propanamide, 2-amino-N-[(1R)-2-[1,2-dihydro-1-(methylsulfonyl)spiro[3H-indole-3,4'-piperidin]-1'-yl]-2-oxo-1-[(phenylmethoxy)methyl]ethyl]-2-methyl-, monomethanesulfonate (9CI) (CA INDEX NAME)

CM 1

CRN 159634-47-6

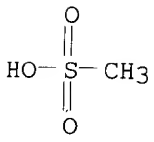
CMF C27 H36 N4 O5 S

Absolute stereochemistry.



CM 2

CRN 75-75-2
CMF C H4 O3 S



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L3 115 S IBUTAMOREN? OR L163191 OR L()(163191 OR 163 191) OR MK677 OR
L4 148 S L2,L3
L5 25 S L4 AND (PD<=19960228 OR PRD<=19960228 OR AD<=19960228)
L6 22 S L5 NOT (127:257642 OR 127:149410 OR 123:74929)/DN

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